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Aims and Scope

Phlebolymphology **is an international scientific journal entirely devoted to venous and lymphatic diseases.**

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology **is scientifically supported by a prestigious editorial board.**

Phlebolymphology **has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.**

Phlebolymphology **comprises an editorial, articles on phlebology and lymphology, reviews, and news.**

Correspondence

Editorial Manager
Hurrem Pelin YALTIRIK
Servier Affaires Médicales
35, rue de Verdun,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 38 98
Email: hurrem-pelin.yaltirik@servier.com

Publication Director
Christophe CHARPENTIER
Suresnes, France

Publisher
Les Laboratoires Servier
50, rue Carnot,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00

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Content

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Editorial

Dear Readers,

In this new issue of *Phlebolymphology,* you will find an original concept of scientific discussion based on clinical cases. These cases cover a wide range of venous pathology and were prepared by international experts within the Vein Inception Programme. This program aims to increase awareness of chronic venous and hemorrhoidal diseases (CVD and HD) and their management over time. All cases come from real clinical practice and represent the need for multidisciplinary involvement in diagnosis and treatment. This original approach includes an opinion expressed by each participating expert on every clinical case presented. So, you may find different and possibly opposing practices, all based on scientific evidence and clinical experience.

The first case presented by **G. GEROULAKOS, A. POULOU, and E. AVGERINOS** ***(Greece)*** discusses the role of nonthrombotic iliac vein lesion in the development of progressive CVD with low response to the standard treatment for superficial reflux. The main question for the discussion is about what patients with varicose veins should be assessed for proximal venous obstruction.

The second case presented by **M. JOSNIN** ***(France)*** is dedicated to the natural history of varicose vein progression in women. Experts discuss different sex-based specifications of the treatment for superficial reflux according to the patient's age: from maidenhood when she takes contraceptive pills, through adulthood when she plans another pregnancy, to elderly age when she receives oral anticoagulants.

The third case presented by **C. D. KAN** ***(Taiwan)*** is focused on a challenging combination of nonthrombotic iliac vein lesion and idiopathic thrombocytopenic purpura. Experts discuss the possibility of vein stenting and strategies for further antithrombotic treatment, considering bleeding risk.

The fourth case presented by **K. LOBASTOV and A. AKULOVA** ***(Russia)*** discusses the strategy of pelvic congestion syndrome treatment in the presence of chronic inferior vena cava obstruction. Experts express different opinions on the feasibility of embolization of gonadal veins in the presence of untreated obstruction, options for conservative treatment of pelvic pain, the impact of pelvic congestion syndrome on fertility, and the strategy of pregnancy management.

The fifth case presented by **N. NIKOLOV** ***(Bulgaria)*** is dedicated to the treatment of a recurrent venous leg ulcer in the patient with a combination of postthrombotic iliac vein occlusion and superficial venous reflux. Experts discuss the optimal sequences of interventions on deep and superficial veins, a strategy of antithrombotic treatment after venous stenting, and the efficacy of conservative treatment of venous ulcers in deep vein obstruction.

The sixth case presented by **Z. T. MEZALEK** ***(Morocco)*** is focused on the prevention of postthrombotic syndrome in patients with iliofemoral deep venous thrombosis. Experts discuss the role of endovascular thrombectomy, compression therapy, anticoagulants, and venoactive drugs in preventing postthrombotic syndrome. They also touch on the pathogenesis of the syndrome and the ambiguity of diagnostic methods.

Enjoy reading this issue!

Co-Editor

Dr Kirill Lobastov

Vein Inception Programme

VIP group experts

Matthieu Josnin,[1] MD, PhD
France

George Geroulakos,[2] MD, PhD
Greece

Kirill Lobastov,[3] MD, PhD
Russia

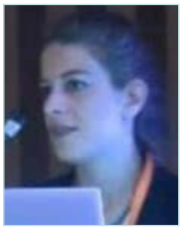
Zoubida Tazi Mezalek,[4] MD, PhD
Morocco

Nadelin Nikolov,[5] MD, PhD
Bulgaria

Chung-Dann Kan,[6] MD, PhD
Taiwan

Other contributing experts

Olga Dzhenina,[7] MD, PhD
Russia



Aikaterini Poulou,[2] MD, PhD
Greece

Efthymios Avgerinos,[2] MD, PhD
Greece

Anastasia Akulova,[8] MD, PhD
Russia

1. St Charles Clinic, Department of Vascular Medicine Interventional Phlebology Unit Wound Care Center, La Roche-sur-Yon, France. **2.** Department of Vascular Surgery, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece. **3.** Pirogov Russian National Research Medical University, Moscow, Russia. **4.** Department of Clinical Hematology – Internal Medicine, Mohammed V University, Ibn Sina Hospital, Rabat, Morocco. **5.** Department of Vascular Surgery, National Heart Hospital, Sofia, Bulgaria. **6.** National Cheng Kung University Hospital, Department of Surgery, Tainan, Taiwan. **7.** First Phlebological Center, Moscow, Russia. **8.** Central Clinical Hospital "Railway-Medicine", Moscow, Russia.

The role of a multidisciplinary approach to the management of chronic venous disease

Kirill Lobastov,[1] MD, PhD; George Geroulakos,[2] MD, PhD; Matthieu Josnin,[3] MD, PhD; Chung-Dann Kan,[4] MD, PhD; Nadelin Nikolov,[5] MD, PhD; Zoubida Tazi Mezalek,[6] MD, PhD; Olga Dzhenina,[7] MD, PhD; Aikaterini Poulou,[2] MD, PhD; Efthymios Avgerinos,[2] MD, PhD; Anastasia Akulova,[8] MD, PhD

1. Pirogov Russian National Research Medical University, Moscow, Russia. **2.** Department of Vascular Surgery, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece. **3.** St Charles Clinic, Department of Vascular Medicine Interventional Phlebology Unit Wound Care Center, La Roche-sur-Yon, France. **4.** National Cheng Kung University Hospital, Department of Surgery, Tainan, Taiwan. **5.** Department of Vascular Surgery, National Heart Hospital, Sofia, Bulgaria **6.** Department of Clinical Hematology – Internal Medicine, Mohammed V University, Ibn Sina Hospital, Rabat, Morocco. **7.** First Phlebological Center, Moscow, Russia. **8.** Central Clinical Hospital "Railway-Medicine", Moscow, Russia

INTRODUCTION

Chronic venous disease (CVD) is a prevalent condition and one of the most common vascular disorders in the world. According to the results of a recent meta-analysis of epidemiological studies, CVD could be found in 67% of the general population, represented by the following CEAP (clinical-etiological-anatomical-pathophysiological) clinical classes: C0s in 9%, C1 in 26%, C2 in 19%, C3 in 8%, C4 in 4%, C5 in 1%, and C6 in 0.42%.[1] Indeed, such prevalent pathology could consume up to 2% of the health care budgets of Western countries.[2] CVD may be represented by venous symptoms like pain or aching, throbbing, tightness, heaviness, fatigue, sensation of swelling, cramps, itching, restless legs, tingling, heat or burning sensation, venous claudication and signs like telangiectasias, reticular veins, varicose veins (VVs), edema, dermatitis, skin hyperpigmentation, induration and atrophy, and healed and open venous ulceration underlined by deep or superficial venous reflux or obstruction.[3-5] Besides lower-limb CVD, specific attention is required for pelvic venous disease (PVD), which can lead to pelvic congestion syndrome (PCS) development in men and women, perineal and genital varicosities, and renal and fertility complaints.[6] Considering a broad spectrum of clinical symptoms and signs that may significantly affect the quality of life (QOL), treatment of individual CVD and PVD cases may require the input of different medical specialists: surgeons and vascular surgeons, angiologists and phlebologists, intervention radiologists, dermatologists and cosmetologists, gynecologists and urologists, hematologists, and others. So, searching for the best treatment option for every individual patient may require a multidisciplinary discussion.

Here, we present 6 clinical cases discussed by the multidisciplinary team to provide the best medical care, putting current scientific evidence at the top while not ignoring each expert's individual experience.

Keywords

chronic venous disease | evidence | expert experience | multidisciplinary | pelvic venous disease | quality of life

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CLINICAL CASE 1.

Diagnostic problems in a symptomatic patient with May-Thurner syndrome

George Geroulakos, MD, PhD
Aikaterini Poulou, MD, PhD
Efthymios Avgerinos, MD, PhD

Department of Vascular Surgery, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece

A 52-year-old male presented a 1-year history of heaviness, dull ache, and swelling from the calf down on both legs. Over the same period, he developed mild punctuated pigmentation on both legs that extended from the ankles to mid-calf, gradually getting worse. There was no previous or current history of deep venous thrombosis. On examination, no varicose veins existed. Circumferential bilateral punctuated pigmentation on the ankles was noticed, being worse on the left lower extremity than on the right lower extremity.

The duplex ultrasound scan *(Figure 1)* showed valvular insufficiency of the left anterior accessory saphenous vein. On the right limb, venous reflux of a perforator vein of the calf was found. The patient underwent endovenous laser ablation therapy (EVLT) of the left accessory saphenous vein under local anesthesia with ultrasound guidance and using a 1470-nm diode laser. The radial fiber was used, and the vein was ablated, applying a linear endovenous energy density (LEED) of 70.92 J/cm, and a total length of 39 cm of the vein was treated. No complications were reported intra- or postoperatively, and the patient was discharged.

However, 8 months later, he returned, presenting deterioration of the pigmentation and stating that the EVLT procedure did not improve his symptoms. On clinical examination, no varicose veins were present, though pigmentation was more intense and extensive on the lower calf and ankles. A computed tomography (CT) contrast venography was performed with the direct puncture of both common femoral veins. Bilateral May-Thurner syndrome (MTS) was diagnosed. *(Figures 2-4)* The patient underwent balloon venoplasty and stenting. Self-expandable, open-cell stents, Wallstents, of 16-cm length and 9-mm diameter, were used *(Figures 5 and 6)*. Cranially, both stents were extended in the inferior vena cava in a double-barrel configuration. The final venography revealed the elimination

Keywords

computed tomography venography | duplex ultrasound | May-Thurner syndrome | pigmentation

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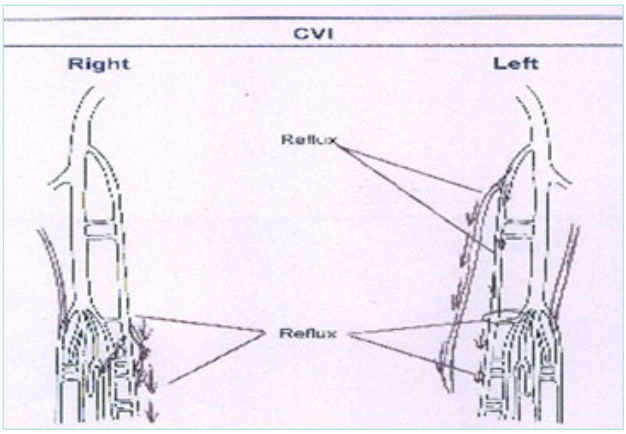

Figure 1. Schematic figure of ultrasound examination.
Abbreviation: CVI; chronic venous insufficiency.

of the venous stenosis in the iliac veins. The patient was discharged on antiplatelet treatment for 6 weeks, and a 6-month follow-up was scheduled. After 6 months, the patient's pain and swelling symptoms were resolved. On examination during the follow-up visit, it was noted that the right calf circumference had decreased from 48 to 46.5 cm. The left calf had decreased from 47 cm to 45 cm. The patient stated that his pain and swelling had completely resolved. A plain X-ray showed no displacement or stent stenosis. Skin pigmentation faded without signs of expansion.

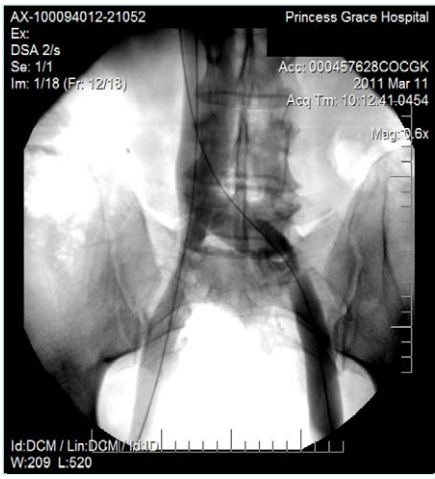

Figure 2. Venography of bilateral May-Thurner syndrome.

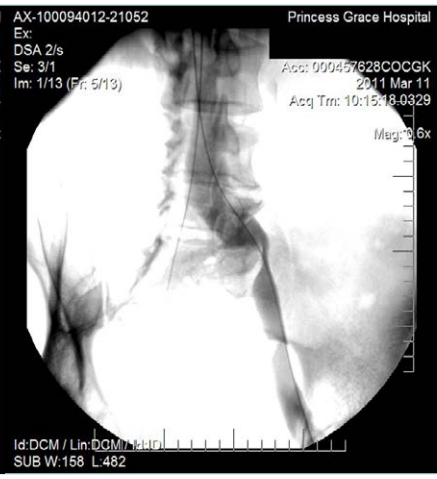

Figure 3. Venography of bilateral May-Thurner syndrome (left side).

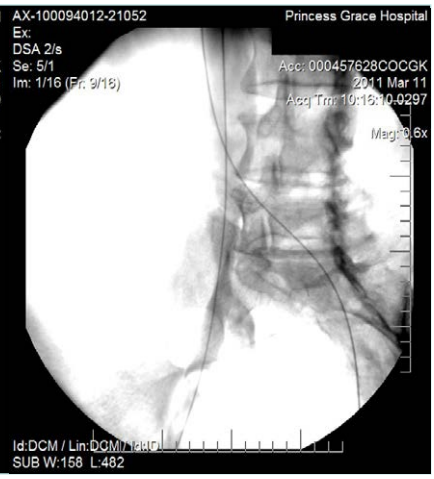

Figure 4. Venography of bilateral May-Thurner syndrome (right side).

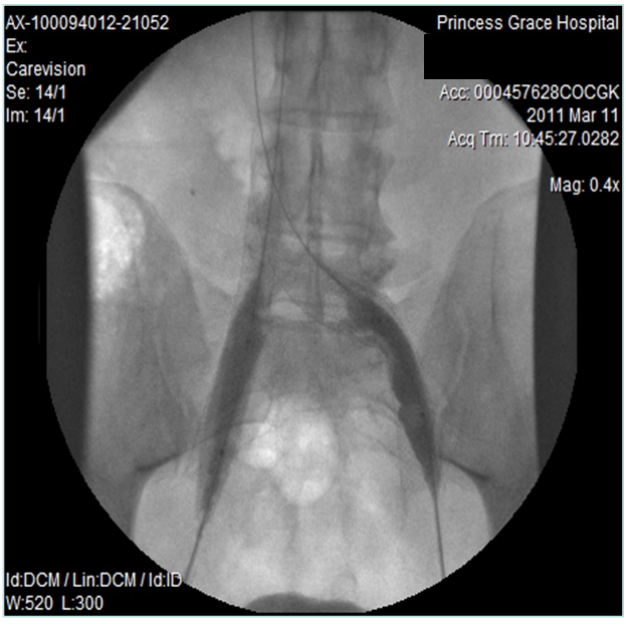

Figure 5. Post dilatation of stents in both iliac veins.

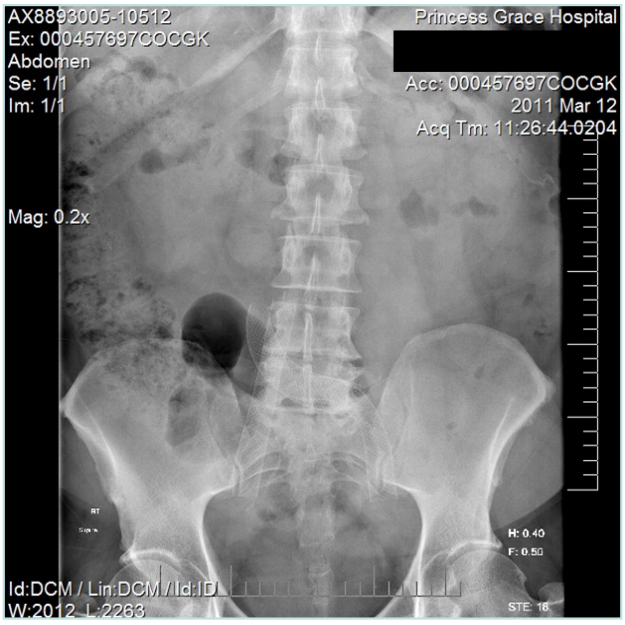

Figure 6. The final results of bilateral iliac vein stenting.

Discussion

What is May-Thurner syndrome, and how often is it found in patients with varicose veins?

Dr Geroulakos. May-Thurner Syndrome (MTS) is also called iliac compression syndrome, where the right common iliac artery against the vertebral body compresses the left common iliac vein.[1] It is a rare condition and may cause edema, varicose veins, deep venous thrombosis (DVT) and subsequent pulmonary embolism, and chronic venous stasis with ulcers.[1,2] Right-sided MTS is also reported in the literature, even if unusual, usually coexisting with left-sided inferior vena cava .[3,4] The majority of MTS cases are left-sided; however, variants include right or bilateral iliac vein compression.[5] More recent advancements in imaging technology reported that up to 20% of the general population has iliac vein obstructive lesions, which are present in patients of all ages and sexes.[6] Bilateral MTS is extremely rare and can be primary, though present in the literature also in cases when iliac artery aneurysms coexist.[7]

The prevalence of MTS (iliac compression syndrome) was reported by Kibbe et al to reach a percentage of 24%, evaluated in an asymptomatic population using computed tomography. However, MTS can cause symptoms when severe and coexisted in 2% to 5% of patients with venous disease.[6] Additionally, Cavalcante et al reported that the percentage of prevalence of MTS increases dramatically when DVT occurs, reaching 49%.[5]

Dr Nikolov. In 1851, Rudolf Virchow first proposed that the increased incidence of venous thrombosis in the left lower extremity resulted from the right common iliac artery compressing the left common iliac vein.[8] In 1908, McMurrich reported that 32.7% of 107 cadavers from an unselected population exhibited obstructions, or adhesions, in the left common iliac vein.[9] However, it was not until 1957 that May and Thurner reported the presence of intraluminal fibrous bands in the left common iliac vein secondary to compression from the right common iliac artery in 22% of the 430 cadavers they dissected and called this finding MTS.[10] Cockett and Thomas were the first to report these findings in patients.[11] Overall, MTS is estimated to cause 2% to 5% of all DVT. However, many retrospective studies have estimated the prevalence to be much higher. Multiple autopsy studies on unselected patients showed MTS prevalence to be between 14% and 32%.[12]

Dr Josnin. Left iliac vein compression syndrome—known as MTS in the United States and Cockett syndrome in Europe—can also be a postural phenomenon that can occur, particularly during pregnancy, when hyperlordosis occurs. The site of compression varies according to the level of the aortic bifurcation.

Apart from the consequences of a postthrombotic syndrome related to a proximal venous thrombosis generated by an MTS, its impact on varicose vein recurrence and chronic venous disease (CVD) predominance on the left limb remains debatable.

Dr Kan. MTS is often associated with symptoms of pelvic congestion and may be associated with varicose veins on the posterior surface of the thigh; it primarily affects young and middle-aged women with a history of multiple pregnancies, during the postpartum period, and those with oral contraceptive use, but many patients are completely asymptomatic.[12] According to Zurkiya's report, the incidence of MTS accounts for about 1.2% (10/763) of patients with venous reflux disorder.[13]

Most people with MTS never have a DVT symptom. They may develop left lower extremity venous hypertension unknowingly. However, a high degree of suspicion is warranted when a young woman develops a left lower extremity DVT in the presence of certain risk factors.

Dr Lobastov. According to the classical definition, MTS is a type of nonthrombotic iliac vein lesion (NIVL) represented by specific fibrotic changes in the vein lumen (spur, obliteration) that occur due to chronic compression and traumatization of the left common iliac vein.[14] It may be found by autopsy in 20% to 30% of unselected cadavers.[10,11,15] However, the prevalence of NIVL may be higher and depends on the screened population, imaging modality, and the diagnostic criteria of obstruction. In the general population without reported symptoms and signs of CVD, NIVLs of >50% may be found by computed tomography (CT) venography in 8.8% to 45%, whereas obstruction of >70% is found in only 0% to 31%.[6,16-21] In one study, NIVL with obstruction of >50% was found in 80% of healthy volunteers by contrast venography.[22] In patients with verified DVT (predominantly left sided) prevalence of NIVL of >50% to 70% is much higher, reaching 15.6% to 80% by CT venography.[16,17,20,23] In individuals with CVD, iliac vein compression of >50% could be revealed by CT venography or intravascular ultrasound (IVUS) in 12% to 53%.[24-28] They occupy an intermediate position between the general population and DVT patients.

Despite traditional notions on the left-side lesion, NIVL in patients with CVD could be found in only 38.7% at the typical point. In comparison, 29.2% of individuals have proximal compression of the right common iliac vein; 7.5%, of the right external iliac vein; and 2.5%, of the left external iliac vein, as revealed by IVUS.[29]

In contrast to classical MTS with morphological intraluminal changes, NIVL is a functional condition that depends on gravity and blood volume. Body position and hydration can affect the vein diameter and degree of obstruction measured by magnetic resonance venography (MRV) and IVUS.[30, 31]

Should patients with hyperpigmentation and skin changes be checked for iliac vein obstruction before surgery on superficial veins?

Dr Geroulakos. The pelvic outflow is rarely routinely investigated in clinical practice, and the findings on an infrainguinal ultrasound scan cannot exclude the presence of a significant proximal obstruction. Avgerinos and Geroulakos have reported the clinical scenarios that raise the index of suspicion and necessitate an investigation of the pelvic venous outflow. These include the presence of a history of DVT, persistent ulcer despite saphenous ablation, significant leg swelling or pain disproportionate to reflux and the extent and size of the varicose veins, deterioration of lipodermatosclerosis, and pigmentation in patients with adequate treatment of superficial venous reflux. These patients should be considered for iliac venous stenting if significant venous stenosis is shown. The improvement in hyperpigmentation after venous stenting for MTS is not adequately documented in the literature.[32]

Dr Josnin. In routine clinical practice, hyperpigmentation alone should not prompt a search for MTS. This may be discussed if it only affects a lower limb. However, in a subject who has never had a DVT and has no pelvic symptoms, if limited to lower-limb symptoms only, venous claudication is the symptom that could by itself justify this search.[33]

Dr Kan. MTS is best diagnosed using the following imaging modalities: duplex ultrasound (DUS), CT venography, MRV, and IVUS. Owing to the advantages of noninvasiveness and no radiation, DUS is the gold-standard diagnostic tool for vascular diseases. High-resolution and 3-dimensional CT venography provides a noninvasive and accurate technique for measuring the degree of left common iliac vein stenosis and has been successfully used to determine the caliber and length of stents needed. It remains the most useful diagnostic tool in our current clinical practice. Compared with CT, MRV requires more time to perform the examination and the time to reconstruct the image is currently longer, it can obtain comprehensive arterial and venous images without using contrast agents and radiation exposure, making it a promising tool for the future. Venography combined with IVUS, which allows for more precise stent placement in the iliac veins and minimizes the risk of developing a jailing effect, is a very informative tool in current practice.[34, 35]

Although DUS is the gold-standard diagnostic tool for vascular disease, reliable imaging of iliac vein tributaries using ultrasound is impossible and, most important, completely unnecessary. According to Zurkiya's report, the incidence of MTS accounts for only 1.2% of patients with venous reflux disorder by ultrasound survey.[13] There is no point in wasting time and effort using ultrasound to identify regurgitation in iliac vein tributaries. However, for specific populations: young and middle-aged women, with significant differences in leg swelling, history of multiple pregnancies, those in postpartum, and those with use of oral contraceptives, further investigation may be required. Suppose a patient presents with hyperpigmentation and skin changes solely due to manifestations of venous reflux disease. Based on current evidence, I do not think routine workup for iliac vein stenosis is warranted.

Dr Nikolov. In everyday practice, NIVL is not routinely investigated. In most cases, we treat varicose veins first, and if there is no improvement, the next step will be to search for deep vein pathology.

Dr Lobastov. Outflow venous obstruction, including NIVL and MTS, has no specific symptoms and signs except for venous claudication.[33] In the study of Raju S et al, among 4026 patients with CVD, examination with IVUS was performed in those with CEAP (clinical-etiological-anatomical-pathophysiological classification) clinical class 3 or higher, significant limb edema, stasis skin changes, ulceration or lower CEAP clinical classes with severe limb pain (≥5 on a visual analog scale) or recurrent cellulitis. Iliac vein obstruction was found in 879 (22%) patients of the total sample, with NIVL in 319 (8%) individuals.[24] A systematic review on venous stenting showed that across all CEAP clinical classes, most often, interventions are performed in limbs with C3 (42%), C4 (22%), and C6 (20%).[36] According to these data, every fifth patient who underwent venous stenting had skin hyperpigmentation, induration, eczema, or atrophy. However, attempts to correlate venous symptoms with NIVL of >50% as detected by MRV in unselected patients who underwent medical imaging for other reasons failed.[37] So, for today, the individual-based suspicion for NIVL and MTS in patients with CVD can be made in those who have venous symptoms and signs that are disproportionate to what would be explained by the DUS findings or in whom a standard conservative or interventional treatment failed.

How specific and sensitive is duplex ultrasound for the detection of iliac vein obstruction?

Dr Geroulakos. DUS is the initial test in evaluating iliac vein obstruction because it is noninvasive, readily accessible, easy to perform, safe, and cost-effective. Labropoulos et al have reported that it is a sensitive method to identify clinically significant vein stenosis.[38] A peak vein velocity ratio of >2.5 across the stenosis is the best criterion for a pressure gradient of ≥3 mm Hg. DUS can be used to select patients for intervention and monitor the treatment's success during follow-up.

Dr Josnin. DUS remains limited in validation of vein stenosis. It is frequently reported in the literature that the figures are overestimated for one main reason: this examination is done in decubitus, and in some patients, the reduction in diameter is physiological.

Dr Kan. The ability of DUS to detect stenosis of the lilac vein is limited. Existing ultrasonographic diagnosis to verify MTS is via observing the shape and appearance of the vein and measuring the blood flow velocity of the iliac vein. However, it may still give us clues to verify iliac vein stenosis or obstruction.

Dr Nikolov. DUS is the most common technique used to diagnose a venous outflow obstruction. However, technical difficulties in assessing the inferior vena cava and iliac veins may limit its utility, especially in the case of compression and stenosis without full occlusion. DUS presented a high agreement with IVUS for detecting venous obstruction of ≥50%. The velocity ratio ≥2.5 is the best criterion for the detection of significant venous outflow obstructions in iliac veins.[39]

Dr Lobastov. Besides the well-known criterion of velocity ratio >2.5 over stenosis, the other ultrasound parameters of NIVL are as follows: the absence of blood flow phasicity (no synchronization with the breathing cycle) and the presence of reflux >2.5 seconds on a common femoral vein (CFV); flow index (the ratio of volume flow on the affected and contralateral CFV) <0.7; velocity index (the ratio of velocity on the affected and contralateral CFV) <0.9; obstruction ratio (the ratio of vein diameter at the point of maximal stenosis and lager distal diameter) <0.5.[38-40] All these criteria have high specificity and low sensitivity that depends on the degree of obstruction. For example, an easily noticeable lack of flow phasicity on CFV is typical for venous obstruction of >80% and rare in less-severe lesions. The presence of reversal flow at the saphenofemoral junction into the epigastric vein is a very specific sign of iliac vein occlusion but could be detected predominantly in postthrombotic vein lesions and not in NIVL.[41-43] Generally, transabdominal DUS of iliac veins in expert hands can provide reliable results compared to IVUS in detecting NIVL and assessing the degree of stenosis.[44] However, in most cases, it should be used to select patients with suspected venous obstruction for further investigation.

What is the best diagnostic approach to verify May-Thurner syndrome?

Dr Lobastov. Since NIVL is a radiological phenomenon that requires interventional treatment in some patients, contrast venography was long used for the final verification of obstruction. However, it appeared to underestimate the presence and severity of venous stenosis compared with IVUS.[45] The last one is considered a reference standard that allows identifying up to 30% more patients with obstruction than multiplanar venography. The sensitivity of CT venography and MRV in comparison with IVUS reaches 97% to 100%, but specificity is lower (57%-86% for CT venography and 23% for MRV).[45] Considering these data, IVUS is a gold standard for NIVL verification when available. If not, noninvasive CT venography and MRV could be used to select patients for venography. However, the extent of morphological lesions detected by IVUS does not always correlate with symptoms and signs of CVD, which raises a question about functional assessment to detect clinically significant venous outflow obstruction.[46]

Dr Nikolov. IVUS is the gold standard to verify MTS. It provides a real-time evaluation of the vessel lumen, the accurate size of the luminal diameter, and information regarding the vessel wall's structural changes. It also provides information about the chronicity of the process, helps in correct implantation of venous stents, and also is contrast free.[47]

Dr Geroulakos. Zymvragoudakis et al prospectively studied 100 consecutive ambulatory outpatients without any history of DVT, presenting to the radiology department for prescheduled abdominal contrast CT for reasons unrelated to venous disease. Patients underwent thorough physical examination, while demographics and a clinical class of the CEAP classification were documented. The diameter and percentage compression of the common iliac vein, compared with the adjacent ipsilateral and the contralateral common iliac vein at the same level, were measured. More than half of the patients presented NIVL as a relatively common anatomic variant, seldom associated with signs and symptoms of CVD.[48] As there is no standard in the prescription of the hemodynamic significance of venous stenosis and as the criterion for stenting is arbitrarily considered to be morphological obstructions higher than 50%, Jayarai et al—supporting that the criterion of 50% stenosis is not helpful for treatment decision-making—proposed a new score, the chronic venous insufficiency score (CCVIS). The CCVIS has a maximum score of 134 and uses a combination of the visual analog scale (VAS) for pain score (range, 0-10), venous clinical severity score (VCSS) (range, 0-24), and the 20-item CVD quality-of-life questionnaire (CIVIQ-20) (range, 0-100).[46] Moreover, due to the uncertainty mentioned above, a large oversizing of 20% in venous stenting is usually chosen, leading to increased wall shear stress and neointimal hyperplasia formation.

Dr Josnin. First of all, it is necessary to standardize the pelvic venous disorders. There is a fundamental inter-relationship between the different pelvic syndromes, and considering them as separate entities often leads to treatment with suboptimal results. Under the aegis of the American Venous and Lymphatic Society, with a great deal of reflection, a consensus of international experts has resulted in a classification system called the Symptoms-Varices-Pathophysiology classification of pelvic venous disorders, thus allowing, like the CEAP that we use, a better understanding and adaptation of treatment for each patient according to what is appropriate for them and for follow-up over time.[49]

Concerning the diagnosis of MTS, CT venography, MRV, or IVUS will reveal intraluminal formations; however, the diagnosis of MTS itself will require the demonstration of a network of collaterals upstream from the left common iliac vein.

Dr Kan. For MTS verification, patients must have detailed history tracking, physical examination, and documentation of CEAP classification, as well as VAS and VCSS scorings. The best method of diagnosis depends on the hospital facilities and equipment available. My hospital can use CT venography and venography with recently added IVUS as our equipment. I prefer to use MRV as a better diagnostic tool, but our magnetic resonance tomography cannot be used for this purpose.

What is the best treatment approach for patients with a combination of May-Thurner syndrome and varicose veins?

Dr Geroulakos. As regards MTS, there is no indication for treatment when asymptomatic. These lesions are permissive,

and typically an additional event needs to occur to manifest clinically. The indication to treat should always be clinically driven. When symptomatic, the fibrotic nature of the disease, per se, is responsible for increased percentages of recoil, resulting in angioplasty alone not being sufficient for treatment.[50]

Therefore, iliac vein stenting is the treatment of choice, as it appears to have excellent long-term patency, minimal morbidity, and satisfactory durable clinical outcome. Wallstents were only available for venous stenting for several years, with excellent results reported by the group of Dr Raju in Jackson, Mississippi.[51] Complications such as migration and compression of the stent's upper end were reported, resulting in reintervention. Lack of radial force at the stent ends collapses the proximal end of the Wallstents and gives a coning configuration when deployed right across the stenosis with no extension in the inferior vena cava.[51] Additionally, ''jailing,'' the impairment of the contralateral flow when a venous stent is extended into the inferior vena cava, increases the risk of contralateral DVT.[52] Raju et al described a technique different from extension in the vena cava to protect the contralateral venous flow by using a Gianturco Z stent deployed on the upper part of the Wallstents. The cumulative primary and secondary patency reported at 24 months were 69% and 93%, respectively. Reinterventions were needed in 11% to fix a malfunction. However, the Z stent seemed to facilitate the bilateral stenting.[53]

The more recent introduction of nitinol venous stents improved some of the limitations of the Wallstents. Nitinol stents do not foreshorten, resulting in more accurate positioning during deployment compared with Wallstents. Moreover, they are more flexible, having a good compression radial force and crush resistance.

Dr Kan. In patients with symptomatic MTS and varicose veins, it is necessary to treat iliac vein disease first. Wallstents and nitinol stents are available with Taiwan Health Insurance. Some physicians have proposed the prophylactic use of bilateral iliac vein stents to prevent the contralateral flow jailing effects, but insufficient data support this view.

Dr Josnin. MTS without intraluminal formations, without venous thrombosis, is a matter of venous compression of the lower limbs.

Dr Lobastov. Venous stenting is a safe and effective procedure to treat chronic venous obstruction, resulting in ulcer healing in 70% of all patients.[54,55] The other outcomes, like improvement in symptoms, disease severity, and quality of life (QOL), are being poorly reported and are not suitable for meta-analysis. The only available randomized controlled trial (RCT) found advantages of venous stenting compared with the best conservative care in patients with progressive CVD.[56] New dedicated venous stents seem to be as effective as Wallstents, providing relief of venous claudication in 83% to 90% and healing of venous ulcers in 32% to 80% of all patients.[55,57]

In the absence of good evidence, the indications for venous stenting in patients with a combination of superficial reflux and NIVL are still debatable. One study showed that confirmed NIVL does not affect the results of radiofrequency ablation (RFA) of superficial veins, regarding technical efficacy, disease severity, and QOL.[58] In contrast, 2 other trials showed that venous stenting, in addition to endovenous laser ablation therapy (EVLT), improves short-term and long-term outcomes, including ulcer healing and superficial reflux recurrence in patients with confirmed NIVL.[59,60] From another point of view, ablation of superficial reflux in addition to venous stenting of NIVL may be beneficial only in patients with progressive CVD (CEAP clinical classes of C4-6),[61] or may not provide any advantage in persons with postthrombotic iliac vein lesions.[62,63]

Considering all these data, venous stenting in patients with symptomatic NIVL should be suggested in progressive CVD (C3-6) when conservative treatment and ablation of superficial veins does not result in sufficient clinical improvement. In noncomplicated CVD (C0-2), ablation of superficial reflux should be considered only irrespective of NIVL, which may be a variation of individual anatomy.

What medical treatment is required after venous stenting for May-Thurner syndrome?

Dr Geroulakos. With regard to anticoagulation and antiplatelet therapy after venous stenting for nonocclusive disease, there is no evidence-based strategy, and such treatment is still under debate. Mahnken et al recommended continuous anticoagulation with warfarin to a target international normalized ratio (INR) range of 2.5-3.0, though there are no evidence-based studies about this.[64] However, that target mainly takes into consideration postthrombotic lesions more vulnerable to restenosis. Long-term warfarin is recommended when extended occlusions, thrombophilia, suprarenal occlusions, and poor outflow in angiogram exist.[65,66] Meissner reported that antiplatelets seem most appropriate for primary nonocclusive iliac vein lesions, likewise for venous grafts when used in the arterial system; however, anticoagulants play a better role in postthrombotic disease.[67] The latter seems to concur with our strategy of antiplatelet therapy for at least 6 weeks post venous stenting for nonocclusive venous disease. Still, the role of antiplatelets has been highly debated in recent literature. Tran et al, in their recent retrospective study, subcategorized the cases of stented NIVL according to the type of anticoagulation treatment received postoperatively for 90 days. The 3 regimens were as follows: i) double antiplatelet (aspirin and clopidogrel); ii) clopidogrel alone; and iii) apixaban/rivaroxaban. In-stent stenosis by DUS was observed, and freedom from in-stent stenosis in 52 weeks was 80.03%, 80.95%, and 83.18%, respectively, with no statistically significant difference between therapy groups.[68]

On the other hand, in the international Delphi Consensus, with accepting the absence of controlled trials for the use of anticoagulants and antiplatelets following venous stenting, Milinis et al stated that anticoagulation is preferable to antiplatelets for the first 6 to 12 months after stenting an NIVL.[69] Of all experts, 72% preferred anticoagulation to antiplatelet therapy following venous stent placement for

NIVLs. The recommendation for life-long antiplatelet therapy after anticoagulation is stopped did not achieve consensus. Also, low molecular weight heparins (LMWH) were stated as the anticoagulant of choice for the first 2 to 6 weeks after stenting.

Dr Josnin. Since the 1990s, endovenous treatments have largely supplanted surgery, which is now reserved for use when previous techniques fail. In the 6 months following treatment, patients remain at risk of thrombosis, justifying an antiplatelet or anticoagulant therapy. There is no validated consensus to date, but direct oral anticoagulants (DOACs) are increasingly used. Long-term patency rates remain satisfactory at around 80% to 90%.[70]

Dr Kan. Venous stenting has become a standard treatment for central deep venous outflow obstructions and postthrombotic syndrome. After a venous stent is placed, maintaining a healthy diet and exercise regimen, taking medications to prevent blood clots, avoiding strenuous activity for some time, and regular follow-up are essential to keep the venous stent patent. After successful recanalization and stenting, stent patency is endangered by in-stent thrombosis and recurrent venous thromboembolism (VTE). Antithrombotic therapy might reduce stent patency loss. The mean primary patency rate of venous stenting with antithrombotic drugs is 82.3% at 1 year and 73.3% 2 years after intervention. Still, there are no specific recommendations on the optimal drug-combination strategy after venous stent placement.[71]

The value of peri-interventional antithrombotic therapy for optimal long-term outcomes can be inferred from Virchow's triad. Most previous studies used vitamin K antagonists (VKA) concomitant with LMWH, but recent trials increasingly used DOAC for the treatment. However, as well known, the recurrence rates are significantly lower in patients with nonthrombotic lesions than in patients with previous thrombosis. Therefore, strategies for anticoagulation and antiplatelet therapy after venous stenting for nonocclusive diseases should take into account the essence of the disease. Treating venous disease should differ from coronary or peripheral artery disease based on blood flow velocity and endothelial properties. To prolong patency, I would prefer triple therapy of aspirin and clopidogrel (dual antiplatelet) with apixaban or rivaroxaban for at least 1 month, even if there is no clear evidence yet.

Dr Nikolov. The patency rates, disease prognosis, and need for antithrombotic therapy primarily depend on the nature of iliac vein lesions. In NIVL, there is no evidence to justify prolonged anticoagulation because the risk of thrombosis is very low.[72]

Dr Tazi Mezalek. In recent years, there has been a growing interest in endovascular stenting of the iliofemoral vein to improve symptoms related to proximal venous obstruction. Maintaining the long-term patency of the stent is one of the main challenges. Published data on the safety and efficacy of the procedure come primarily from cohort studies that focused mainly on mechanical aspects related to stent placement and flow. The impact of the choice and duration of antithrombotic treatment has not been specifically studied. Although antiplatelets have been shown to be beneficial in preventing restenosis of arterial stents, these effects cannot necessarily be extrapolated to venous stents since the generation of thrombin drives venous stent thrombosis.[69] Additionally, in an experimental porcine model, McBane et al demonstrated that aspirin and clopidogrel did not prevent stent vein thrombosis, unlike the inhibitor of factor Xa, which completely inhibited venous stent thrombosis.[73] Dual antiplatelet plus DOAC exposes patients to a high risk of bleeding without evidence of benefit. Our opinion is to maintain a full dose of oral anticoagulant (preferably DOAC) for long-term treatment.

Dr Lobastov. According to a recent systematic review, stent patency depends on the type of primary lesion (nonthrombotic, postthrombotic, acute DVT) but is not affected by the type and duration of antithrombotic therapy.[71] Undoubtedly, stenting in the settings of DVT and postthrombotic syndrome requires prolonged anticoagulation, predominantly with DOACs. In contrast, NIVL seems to be a benign disease with the lowest risk of in-stent thrombosis and stenosis, so prolonged anticoagulation is not obligatory. The recent systematic review suggests that 3 to 6 months of antiplatelet treatment may be enough after stenting of an NIVL.[74]

Is MPFF indicated for patients with May-Thurner syndrome?

Dr Kan. Micronized purified flavonoid fraction (MPFF) can improve venous tone and capillary permeability, but the exact mechanism of action of the drug remains unclear. MPFF has anti-inflammatory, antioxidant, and powerful free-radical scavenging properties. MPFF decreases the expression of adhesion molecules by neutrophils and monocytes in patients with CVD. Based on the experimental results of MPFF usage in chronic venous hypertension, MPFF treatment was found to significantly prevent capillary rarefaction and initiation of the venous inflammatory cascade.[75] Summarized results of cohort studies show the hemodynamic and clinical benefits of MPFF. It can normalize the diameter of the great saphenous vein and abolish afternoon reflux, night cramps, evening heaviness, and pain, decreasing the intensity of leg pain (measured using a VAS) and improving QOL.[76]

MTS is also a CVD, a complex condition characterized by chronic inflammation and remodeling of the venous wall, resulting in valve damage, reflux, and venous hypertension. Chronic inflammation eventually affects microcirculation, producing skin changes and ulceration. MPFF improves venous tone and increases lymphatic drainage and can be used alone in the early stages or as an adjunct to surgery, sclerotherapy, endovenous thermal ablation, or compression. After venous stenting, the use of MPFF is not contraindicated. Therefore, I would still use MPFF as an adjunct therapy for patients with May-Thurner syndrome.

Dr Josnin. By analogy with the validated and recommended indications for CVD, in particular by the latest recommendations of the European Society for Vascular Surgery, the use of MPFF in symptomatic patients is indicated.[77] The pharmacokinetics and mode of action of the molecule have been well described and its efficacy demonstrated. To the best of my knowledge,

there is no study in the literature specifically about its use in MTS, but there are many articles on chronic pelvic pain, particularly in pelvic congestion syndrome. Although the continuum between the different pathophysiological entities is sometimes difficult to define, an improvement in QOL and in severity of pathology was recently shown in women with pelvic congestion syndrome.[78]

Dr Lobastov. MPFF is a well-studied drug that demonstrated high efficacy in CVD of all clinical classes.[79] It significantly improves individual symptoms, signs, and QOL, reduces edema, redness, and skin changes, and accelerates the healing of leg ulcers.[80, 81] It can be used in adjunct to open surgery and endovenous treatment to improve functional and aesthetic outcomes.[82] Despite the absence of direct evidence of MPFF use in NIVL or MTS, the drug is still indicated to treat venous symptoms and signs of CVD before, after, or instead of stenting. Considering the prevalence of NIVL in a population of patients with CVD, it can be assumed that many individuals with venous obstruction participated in the trials with MPFF and achieved positive results. Moreover, in the only RCT with stenting, pain at 6 months after intervention reduced from a score of 9 to 2.5, and VCSS decreased from 18.5 to 11.0.[56] So, even after interventional treatment, patients still had indications for MPFF due to the persistence of venous-specific symptoms and signs. Of course, the role of adjunctive pharmacological therapy in obstructive venous disease should be evaluated in specific trials.

Conclusion

- NIVL is a widespread condition in the general population and among patients with CVD that not always needs to be confirmed and treated. MTS is a type of NIVL with intraluminal fibrotic changes (spurs) in the common iliac vein, and it may be responsible for the development of CVD with skin changes.
- Investigation for venous outflow obstruction is not necessary for all CVD patients. The individual-based suspicion for NIVL and MTS should be made in those who have venous symptoms and signs that are disproportionate to what is explained by DUS findings or in whom a standard conservative or interventional treatment failed. This particularly includes patients with persistent ulcers despite saphenous ablation; significant leg swelling or pain disproportionate to reflux, the extent and size of the varicose veins; deterioration of lipodermatosclerosis; and pigmentation with adequate treatment of superficial venous reflux.
- DUS of femoral and iliac veins can be used as a first approach to detect patients with suspected NIVL. CT venography, MRV, and IVUS should verify the obstruction. IVUS is the reference standard to confirm NIVL, assess its degree, and assist with stenting.
- In patients with combined NIVL and superficial reflux, the efficacy of isolated superficial vein ablation is controversial. Adjunct venous stenting should be considered in those with progressive CVD (C3-6), especially when conservative treatment and superficial ablation are not effective.
- The type and duration of antithrombotic therapy after stenting of NIVL is under debate. Emerging evidence suggests that single antiplatelet therapy may be sufficient for 3 to 6 months. However, many experts and practitioners still prefer treatment with VKA and DOACs for 6 to 12 months.
- MPFF in NIVL and MTS is indicated to treat symptoms and signs of CVD before, after, or instead of venous stenting.

CORRESPONDING AUTHOR

George Geroulakos

Attikon University Hospital of the National and Kapodistrian University of Athens, 1 Rimini Street, Haidari, 124 62 Athens, Greece

EMAIL: *ggeroulakos@med.uoa.gr*

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CLINICAL CASE 2.

The natural history of varicose vein progression

Matthieu Josnin, MD, PhD

St Charles Clinic,
Department of Vascular Medicine
Interventional Phlebology Unit
Wound Care Center,
La Roche-sur-Yon, France

This is an evolving clinical case in a patient first presenting at the age of 20, followed through the age of 75. We will start with the first consultation where the patient, aged 20 years, consulted you for the first time with the main reason being occasional discomfort along the inner side of the right lower limb during prolonged standing, especially in summer. The patient had no children, no particular history apart from a family history of chronic venous disease (CVD) affecting both her parents, and she was on hormonal contraception. Further questioning revealed that these complaints dated back to her 12th birthday and had been attributed to growth by her parents and her family doctor. Clinically, the patient was free of skin changes, and a visible varicose tributary was found on her leg. The examination resulted in the following mapping: clinical, etiological, anatomical, pathophysiological (CEAP) classification C2sEpAs2,3,5Pr *(Figure 1)*.

This patient consulted you again at the age of 35 years old. She had not been treated for her varicose veins, and she had 2 pregnancies that were carried to term but with symptoms that have deteriorated. The vein diameters had increased in the great saphenous vein (GSV) (+1 mm) and the tributaries, which became more numerous and dilated. She had ankle edema. She wished to have a third child and asked for your advice on treating her GSV. You performed an ultrasound examination, resulting in the following mapping: C3sEpAs2,3,5Pr *(Figure 2)*.

Finally, it was decided not to treat this patient. She had been offered endovenous laser ablation therapy with ultrasound-guided foam sclerotherapy of her tributaries, but due to family reasons, she did not return for intervention. She was advised to wear compression stockings as regularly as possible and to continue taking venoactive drugs, especially since the edema reinforced her indication.

Keywords

great saphenous vein | hormonal contraceptive | pregnancy | varicose vein

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Finally, time passed. The patient, now 75 years old, returned to consult you with painful inflammatory dermatitis of the right ankle *(Figure 3)* and permanent ankle and leg edema. She is being treated for atrial fibrillation with rivaroxaban 20 mg once daily.

Your examination found a GSV insufficiency with a diameter of 9 mm and tributaries of 5 mm that are going to the area of inflammatory and pigmented dermatitis. Her CEAP classification is C3,4asEpAs2,3,5Pr *(Figure 3)*.

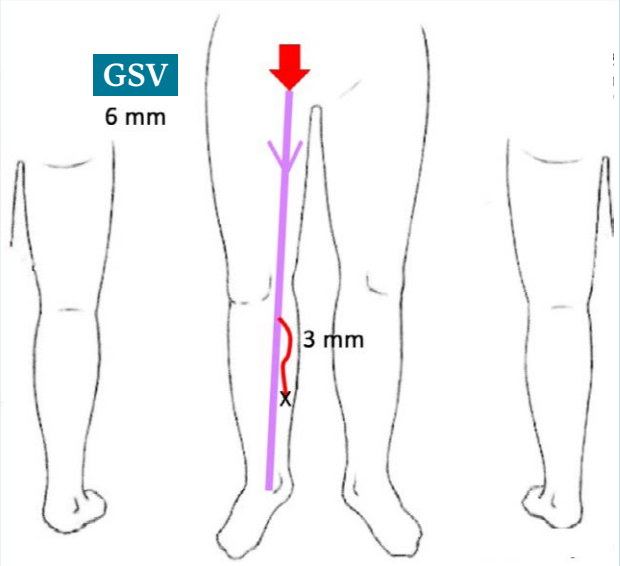

Figure 1. The patient at the age of 20 years old. A schematic showing incompetent right great saphenous vein (GSV) of 6 mm at the thigh level and a varicose tributary of 3 mm at the calf level.

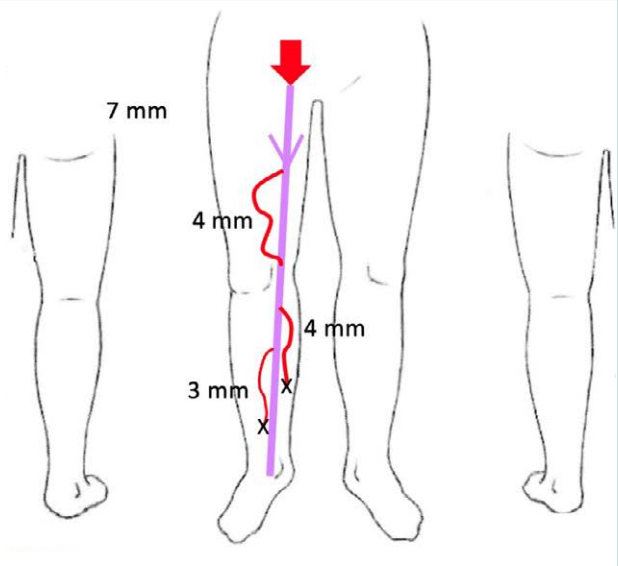

Figure 2. The patient at the age of 35 years old. A schematic showing incompetent right great saphenous vein (GSV) of 7 mm at the thigh level and varicose tributaries of 3-4 mm at the thigh and calf levels.

Discussion

What is the risk of varicose vein progression in a young woman?

Dr Geroulakos. Risk factors for the progression of varicose veins include advanced age, obesity, sedentary lifestyles, occupation, family history, and pregnancy. Varicose veins are associated with vein wall inflammation; however, the precise etiology of the inflammation is unclear. When varicose veins develop, these can progress through cycles of inflammation and leukocyte recruitment, leading to further deterioration of vein walls and valves, increased hypertension, and the release of additional proinflammatory mediators. Early treatment of symptomatic varicose veins and lifestyle changes can help break the inflammatory cycle and improve symptoms.

Dr Kan. Sometimes, we feel that women are more prone to have varicose vein symptoms than men. In fact, varicose veins are almost as common in women as in men, but spider veins are more common in women. Varicose veins may be completely asymptomatic and cause no health problems. Based on findings from the Edinburgh Vein Study, a population-based cohort study, we know that over 13 years, nearly half of the general population with chronic venous disease (CVD) worsened, and almost a third of those

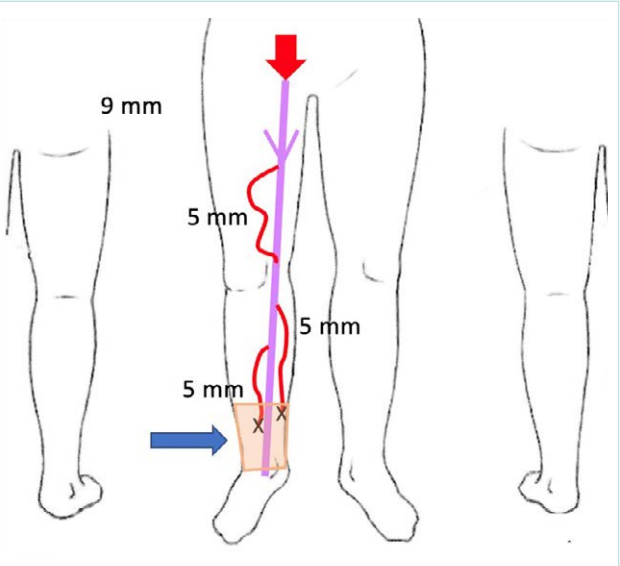

Figure 3. The patient at the age of 75 years old. A schematic showing incompetent right great saphenous vein (GSV) of 9 mm at the thigh level, multiple varicose tributaries of 5 mm at the thigh and calf levels, and zone of dermatitis at the ankle.

with varicose veins developed chronic venous insufficiency (CVI) skin changes, with an increase in their risk of ulcer disease. The annual progression rate is 4.3%. In nearly half of the patients with exacerbations, the disease progressed in one leg (affecting both as well), whereas in one-third of

cases, it progressed in both legs; and in one-fifth of cases, unilateral disease progressed to bilateral disease, but the original diseased leg did not deteriorate. Age, family history of varicose veins, history of deep venous thrombosis (DVT), overweight, and superficial or deep reflux may affect the risk of progression. A family history of varicose veins and a history of DVT were the only 2 baseline factors independently associated with an increased risk of progression.[1]

Dr Nikolov. The data suggest reflux progression may develop from segmental to multisegmental superficial reflux. At younger ages, reflux in tributaries and nonsaphenous veins is more frequent. During a 13.4-year follow-up period, 57.8% (4.3%/year) of all CVD patients showed progression of the disease.[1] Annual progression rates of approximately 4% have been reported for the Edinburgh Vein Study, the Bonn Vein Study, and reviews of other epidemiological studies. In the Edinburgh Vein Study, the overall progression rate was 58% after a follow-up of 13 years. The main risk factors for progression in patients with varicose veins at baseline were age over 55 years (odds ratio [OR], 3.9; 95% confidence interval [CI], 1.1–14.3), overweight/obesity (body mass index [BMI], ≥25; OR, 1.9; 95% CI, 1.1–3.1), and a family history of varicose veins (OR, 1.9; 95% CI, 1.20–3.04). Additional risk factors included female sex and superficial venous reflux.[2,3]

Dr Tazi Mezalek. Nearly half of the general population with CVD deteriorated during 13 years, and almost one-third with varicose veins developed skin changes of CVI, increasing their risk of ulceration.[1] A randomized controlled trial (RCT) called the REACTIV trial (Randomised and Economic Assessment of Conservative and Therapeutic Interventions for Varicose Veins) confirmed that patients randomized to the best medical treatment (graduated compression stockings) had a worse quality of life (QOL) after 2 years than patients randomized to the interventional (sclerotherapy, open surgery) treatment of their varicose veins.[4] The risk of progression might be influenced by age, family history of varicose veins, history of DVT, overweight, and superficial reflux, especially in the small saphenous vein and with deep reflux.

Dr Lobastov. There is conflicting evidence on the prevalence of CVD, CVI, and varicose veins in men and women. According to a recent meta-analysis, women are at higher risk of developing CEAP (clinical, etiological, anatomical, pathophysiological classification system) clinical classes C1-2 (OR, 1.58; 95% CI, 1.53-1.62) and C1-6 (OR, 2.26; 95% CI, 2.16-2.36), but not C4-6 (OR, 1.02; 95% CI, 0.97-1.08).[5] The main problems of such assessment are that women more often seek medical care for early-stage CVD (C0-1), and the difference between reticular and varicose veins is not always correctly reported, especially in early epidemiological studies. Parity was suggested as an essential risk factor for the development of CVD, with a positive correlation between the number of pregnancies and the prevalence of C1-2 clinical classes.[5-7] However, fewer studies stated the absence of such a correlation.[8-10] The confounding role of age and ethnicity may be the reason for this inconsistency. The evidence on hormonal contraception is more conflicting with a similar number of studies that find differences or do not.[5]

The progression of CVD is studied better in prospective trials. Combining their results, the annular progression rate may be estimated as 6% to 24% for the detection of new reflux on previously intact venous segments, 24% for the appearance of new varicose veins, 4% to 5% for the progression of C2 to higher clinical classes, 5% for the development of new skin changes, 1% to 1.4% for new ulceration, 1% to 2.9% for superficial vein thrombosis, and 1.4% for bleeding.[11-16] All these figures advocate the treatment of varicose veins at early stages to prevent further progression and complications.

Dr Josnin. The practitioner who sees a young patient with varicose veins must keep in mind that, unlike a man, she may have pregnancies, that she will probably be on the contraceptive pill, and that this, in case of evolution of her venous disease, will expose her to the risk of venous thromboembolism (VTE). Prevention must take precedence over treatment if it is not immediately necessary, regardless of the patient's sex. However, wearing compression stockings throughout pregnancy will be imperative for this patient if she has not taken care of her varicose veins and if they have evolved. It is also important not to rely on being able to foresee the evolution of the disease to recommend that the patient return for another visit and to give advice about what should lead the patient to seek consultation (eg, an increase in the symptoms, increase in the size of the varicose veins, skin changes).

What treatment may be suggested for young nulliparous women taking hormonal contraceptives?

Dr Geroulakos. If the QOL is affected by symptomatic varicose veins, then endovenous thermal ablation with phlebectomy under local anesthesia should be considered.

Dr Kan. Most varicose veins in young, nulliparous women do not have severe symptoms. Even those valvular varicose veins alone or as part of pelvic congestion syndrome (PCS) are rare. In adolescent patients with severe symptoms, a comprehensive clinical examination, duplex ultrasound (DUS), contrast venography, and magnetic resonance venography (MRV) should be performed to rule out other diagnoses. Imaging results confirmed the presence of large venous lakes. Note the venous drainage to the internal iliac vein and connection to the great saphenous vein (GSV). Attention also should be paid to ovarian or internal iliac veins or their major tributaries for insufficiency, dilation, or reflux. Since no obvious symptoms exist, most patients do not require any intervention during this period. Two major factors guiding intervention decisions or not are symptoms and their association with PCS or leg varicose veins. Designing a treatment plan is important for any venous circulation disorder that has been identified by imaging. Advanced imaging of the pelvic and leg veins should be obtained to guide treatment, including compression, sclerotherapy, embolization, or surgical ligation.

Dr Lobastov. Considering the risk of CVD progression, endovenous ablation may be offered for adult women of any age. The most effective approach is EVLT or radiofrequency

ablation (RFA) of the GSV trunk.[17] At the same time, isolated ablation of varicose tributaries with mini-phlebectomy or sclerotherapy with preservation of the GSV trunk may be an option at the early stages of CVD, considering a small diameter of the vein.[18,19] In terms of GSV preservation, a hemodynamic approach with classical open or endovascular CHIVA (*Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire* [Conservative and Hemodynamic treatment of Venous Insufficiency in outpatients]) may be discussed as having the lowest rate of recurrence.[20,21] According to the continuous use of estrogen-containing oral contraceptives, no good evidence of the safety of endovenous ablation is available. The recent consensus on sclerotherapy suggests individual assessment of VTE risk, making a decision for estrogen cessation case by case, and avoiding intervention in women at high VTE risk and known thrombophilia.[22]

Dr Dzhenina. A woman's QOL can be the starting point for deciding on surgery. Suppose existing varicose veins reduce the QOL due to venous symptoms or a cosmetic defect. In that case, neither the patient's young age nor the absence of previous pregnancies should deny the intervention. In addition, long-term use of hormonal contraceptives may affect the progression of CVD.[23] Moreover, using oral contraceptives in the background of varicose veins may be associated with an increased risk of VTE by 2 to 6 times for DVT and 1.4 to 5.6 times for superficial venous thrombosis (SVT).[24]

When planning endovenous ablation or open surgery, it should be taken into account that estrogen-containing contraceptives (not only oral pills but also vaginal rings and transdermal systems) are considered an independent VTE risk factor. According to the World Health Organization (WHO) eligibility criteria for hormonal contraceptive use, minor surgery does not require cessation of hormonal contraception.[25] However, there is currently no evidence of the safety of endovenous ablation in the background of contraceptive pills. It seems appropriate to assess the global VTE risk, considering use of hormonal contraceptives. The essential issue is that early discontinuation of oral contraceptives (as indicated for major surgery by WHO) is associated with a high risk of adverse events. After the resumption of treatment, the risk of VTE increases dramatically, as in the case of first usage (''the new user effect'').[26,27] So, the risk of postoperative VTE in such patients combines the effect of intervention by itself and the ''new user effect'' if hormonal contraceptives were stopped before surgery and resumed after it. Regarding these facts, it seems safer and more comfortable for women not to stop hormonal contraceptives before endovenous ablation but to use pharmacological prophylaxis of VTE according to the individual risk. The assessment should consider contraceptive pill usage. That's why the Caprini score looks most appropriate.[28]

Dr Josnin. The treatment chosen was the wearing of compression stockings and taking VAD, particularly during flare-ups and in the summer period, as recommended because of her symptoms. These recommendations have prevailed since 2008 and were recently updated by the European Society of Vascular Surgery, which suggests this course of action with grade IIA: ''For patients with symptomatic CVD, who are not undergoing interventional treatment, are awaiting intervention, or have persisting symptoms and/or edema after the intervention, medical treatment with venoactive drugs (VADs) should be considered to reduce venous symptoms and edema, based on the available evidence for each individual drug.''[29-32]

The issues that may arise for the practitioner in deciding whether to remove the GSV are that the patient has never had a child, the symptoms are not very marked, and she is young. These arguments are, however, to be discussed as they have long prevailed. The National Institute for Health and Care Excellence (NICE) recommendations regarding the diagnosis and management of varicose veins insist on one point. However, they stipulate that they do not cover the spectrum of the child.[33]

What is the risk of complications of varicose veins during pregnancy if untreated?

Dr Geroulakos. Pregnancy is considered a major risk factor in women's increased incidence of varicose veins, leading to venous reflux and leg edema. The most common symptom of varicose veins and edema is the substantial pain experienced, as well as night cramps, numbness, tingling, and legs that may feel heavy and achy. Other complications include thrombophlebitis and bleeding.

Dr Kan. Pregnancy is thought to be a major contributing factor to the increased incidence of varicose veins in women, which can lead to venous insufficiency and leg edema. The proposed mechanism for pregnancy-induced varicose veins is that the gravid uterus causes compression of the pelvic venous system, resulting in lower-extremity venous hypertension coupled with hormonal changes that lead to increased venous distensibility. Increased parity, excessive gestational weight gain, post-term pregnancy, and preeclampsia affect the development of varicose veins after pregnancy. The most common symptoms of varicose veins and edema are severe pain, nighttime cramping, numbness, tingling, and legs that may feel heavy, sore, and possibly considered unsightly.[7]

Vulvar varicosities, ie, dilated venous channels in the vulvar area, are rare and almost exclusively affect women during pregnancy, but most do not report any symptoms. Nearly 4% to 22% of pregnant women present with vulvar varicosities. Most cases disappear immediately after labor or postpartum, and only 4% to 8% persist or worsen with time. Sometimes, a patient might have complication of hemorrhoids with pain, itching, and bleeding. Varicose veins can be associated with an increased risk of VTE during pregnancy.

Most untreated varicose veins in pregnancy are usually harmless and get better after the baby is born, and most don't need treatment. Also, hemorrhoids are typically benign and may get better after the baby is born.

Dr Lobastov. Despite pregnancy being an established risk factor for varicose veins and CVD, no clear evidence exists on the disease progression and development of complications.

Dr Dzhenina. Pregnancy is a significant risk factor for CVD development in women. In addition to mechanical factors such as compression of pelvic veins by the pregnant uterus and an increase in the circulating blood volume, hormonal changes play a pivotal role. Progesterone negatively affects the collagen and elastin network of the venous wall, contributing to the dilatation of vessels. Parity, short intervals between pregnancies, and leg pain during premenstrual syndrome are the predictors of varicose veins and CVD development in pregnancy.[34-36]

The dilation and tortuosity of superficial veins observed during pregnancy in some women may spontaneously reduce postpartum. But there are no rules to distinguish between physiological changes and CVD development in pregnant women.

When pregnancy occurs in the background of existing varicose veins, the disease progression as development of new varicose veins and appearance or exacerbation of venous symptoms can be expected. However, still, there is no evidence of the speed and frequency of preexisting CVD progression.

Pregnancy is also considered a high-risk factor for VTE in women. The incidence rate is 0.6 to 2.2 cases per 1000 deliveries and tends to have increased in recent decades. Compared with nonpregnant women of childbearing age, the relative risk of VTE increases 7 to 10 times during pregnancy and 15 to 35 times postpartum.[37] Varicose veins are considered an independent minor risk factor in assessing antepartum and postpartum VTE risk by Royal College of Obstetricians and Gynaecologists (RCOG) guidelines.[38] The combination of varicose veins with additional medical or obstetric factors may require pharmacological prophylaxis with low molecular weight heparin (LMWH).

Evidence of a 35-fold increase (95% CI, 19.1–63.8) in the risk of VTE associated with reproductive risk factors, including pregnancy, was observed in women with a history of SVT.[39] However, there are still no reliable data on the frequency of perinatal SVT.

Dr Josnin. The risk of DVT and/or pulmonary embolism increases throughout pregnancy and peaks in the last trimester and postpartum period.[40] The presence of varicose veins requires monitoring and compression stockings. In patients with risk factors for VTE or with a history of venous thrombosis, treatment with LMWH should be introduced. Most varicose veins occurring during pregnancy, including vulvar ones, disappear after pregnancy, which indicates that the patient should be re-evaluated at least 3 to 4 months after delivery.

When is it better to treat varicose veins: before or after pregnancy?

Dr Geroulakos. Patients with varicose veins should be advised to use graduated compression stockings during pregnancy and may be considered for surgical intervention if they have symptoms affecting their QOL at least 6 months postpartum.

Dr Kan. During pregnancy, blood volume increases by 20% to 40% to ensure adequate nutrition for the fetus. In addition, as the pregnancy progresses, the growing uterus increases the pressure on the intra-abdominal and pelvic veins, leading to increased pressure in the leg veins. Treatment before pregnancy is advisable for overt and symptomatic varicose veins to avoid further development of varicose veins during pregnancy, and it ensures greater comfort during pregnancy. Some recurrences that develop can be efficiently dealt with by sclerotherapy after delivery. However, with asymptomatic varicose veins, follow-up and wearing compression stockings during pregnancy may be considered. After pregnancy, we can see the progression of the disease and then decide what to do next.

Dr Tazi Mezalek. Varicose veins affect about 40% of pregnant women. Although varicose veins may appear during pregnancy, pregnant women should be informed that they may regress during the postnatal period. Interventional treatment for varicose veins should not be considered for women during pregnancy unless in exceptional circumstances, such as with the presence of bleeding varicosities.

Dr Lobastov. No good evidence exists concerning this question. Pregnancy can provoke CVD and varicose vein deterioration with the development of complications. Particularly, untreated varicose veins are considered a risk factor for VTE that may require anticoagulation in combination with other factors.[38] Pregnancy can also lead to a rapid recurrence of treated varicose veins. Pregnant women will be recommended to wear compression stockings irrespective of previous intervention.

Dr Dzhenina. When pregnancy occurs after surgical treatment of varicose veins, a recurrence with decreased QOL is possible, requiring the wearing of compression stockings and planning of a second intervention after delivery. With watchful waiting, the onset of pregnancy can provoke the progression of varicose veins, which could accompany an additional decrease in the QOL. It will also require the wearing of compression stockings and planning of intervention after delivery. So, there is no preferred solution. Considering varicose veins as a modifiable risk factor for perinatal VTE, preliminary removal can reduce thrombotic risk and, probably, decrease the need and burden of pharmacological prophylaxis.

Dr Josnin. The NICE recommendations insist on the fact that the consideration of a pregnancy or a new pregnancy should not delay the treatment of varicose veins if the indication has been established and that a delay of 3 to 6 months between a delivery and a treatment of varicose veins is acceptable.[33]

What is the best method for ablating the great saphenous vein and varicose tributaries in middle-aged women?

Dr Geroulakos. There is a general agreement that endothermal ablation is the treatment of choice for the management of saphenous trunks. The management of the tributaries is more controversial. Concomitant phlebectomy

has the advantage of a holistic treatment of the varicose veins on the same admission. Phlebectomies at a second stage increase the cost of the procedure and the inconvenience to the patient, although some may have complete resolution of the varices with the saphenous trunk ablation and may be spared from a second procedure. Sclerotherapy of the tributaries could lead to hyperpigmentation of the skin, a complication most uncommon with phlebectomy, and a higher recurrence rate if their diameter is larger than 6 mm.

Dr Kan. I think the question depends on the country, health care payment issues, and recent developments in technology and equipment. To achieve the purpose of GSV removal, endovenous thermal ablation, nonthermal-nontumescent interventions, and even open surgical ligation with stripping can accomplish this purpose. Both phlebectomy and sclerotherapy can achieve good results for varicose tributaries, but large-scale phlebectomy may require general anesthesia to achieve painless surgical results. Even sclerotherapy can achieve good results, but for large-sized tributaries, sometimes the thrombus formation after sclerotherapy may cause pain and a lumpy feeling, making the patient uncomfortable. I would recommend endovenous therapy, microphlebectomy, and sclerotherapy under local anesthesia as initial treatment.

Dr Lobastov. Considering the current evidence, the best method for GSV ablation is cyanoacrylate embolization (CAE), according to the technical success and postoperative pain level.[17] However, CAE is the most expensive treatment method and associated with hypersensitivity reactions in 6% to 16%.[41-44] In contrast, endovenous laser ablation therapy (EVLT) and radiofrequency ablation (RFA) are equally effective and relatively cheaper than CAE.[41,45] Mechanochemical ablation (MOCA), in turn, is associated with a lower occlusion rate than with EVLT, but does not provide any advantages in perioperative or postoperative pain.[46] Thus, thermal ablation of a GSV trunk with EVLT and RFA is preferable. Varicose tributaries could be removed with microphlebectomy or sclerotherapy simultaneously or in a delayed manner, according to the patient's preferences. Compared with simultaneous treatment, delayed intervention is associated with lower improvement in disease severity and QOL within the first 12 months, although this difference disappears in long-term follow-up. According to a meta-analysis, the staged intervention is required in only 36% of patients after isolated ablation of the trunk.[47]

Dr Josnin. Although the ablation of the GSV trunk by a thermal method is nowadays unanimously recommended, the treatment of tributaries is much less so. The recommendations differ from one country to another. The literature does not allow us to answer the question, especially as no comparative study could be carried out, as the number of arms to be included would be too large: concomitant or deferred intervention, sclerotherapy or phlebectomy, if deferred, for how long, if the absence of treatment, for what end point, from what diameter onwards should treatment be carried out, etc?

In this case, the choice was made to treat the thigh tributary because it was prominent and to leave the calf tributaries to evolve (deferred treatment if necessary).

Does varicose vein surgery differ in older ages, and what approaches are better for elderly patients?

Dr Geroulakos. The effect of endovenous procedures in managing varicose veins is independent of the patient's age.

Dr Kan. I would still recommend endovenous therapy and microphlebectomy with sclerotherapy under local anesthesia as initial treatment for aged patients. But sometimes, in very elderly patients, I would recommend local sclerotherapy or symptomatic compression first.

Dr Nikolov. Regardless of age, thermal ablation techniques are always a first choice. We should consider the nonthermal techniques in selected patients with many comorbidities because they are less invasive and faster to perform than the others.

Dr Lobastov. Modern endovenous ablation methods under local tumescent anesthesia do not have any limitations by age. The efficacy and safety of EVLT and RFA are similar in patients over and younger than 75 years old.[48,49] The patient's mobility and ability to wear compression stockings when indicated are more important than formal age.

Dr Josnin. The patient's age should not interfere with the choice of treatment because it is now accepted by all international recommendations that endovenous treatments under local tumescent anesthesia without sedation or phlebectomy under the same conditions are sufficient in most cases.

Does chronic anticoagulation affect the efficacy and safety of varicose vein surgery?

Dr Geroulakos. In a recent retrospective review, the authors reported that for patients who had undergone endothermal ablation for symptomatic saphenous venous reflux, the periprocedural use of direct oral anticoagulants (DOACs) did not adversely affect the efficacy of endovenous ablation to ≥9 months. Furthermore, DOAC use did not confer additional risk of bleeding, DVT, or endovenous heat-induced thrombosis (EHIT) periprocedurally.[50]

Dr Nikolov. Clinical practice guidelines on the management of CVD of the lower limbs (European Society for Vascular Surgery [ESVS]) stated that it is safe to perform EVLT on anticoagulation therapy.[32]

Dr Tazi Mezalek. There is no link between chronic anticoagulation and bad outcomes for varicose vein surgery.

Dr Lobastov. The current evidence suggests no influence of chronic anticoagulation with vitamin K antagonist (VKA) or DOACs on the efficacy or safety of sclerotherapy, EVLT, and RFA.[50-58] However, performing RFA over oral anticoagulation may increase the risk of technical failure in a short-term follow-up.[55]

Dr Josnin. It was decided to treat the patient as before, and she agreed. It is important to emphasize that anticoagulants do not change the management of these patients. Guidelines emphasize that anticoagulation is not a contraindication but also that the only anesthesia that should be used for thermal endovenous ablation is tumescent anesthesia, with very rare exceptions.[59,60]

Can treatment with micronized purified flavonoid fraction stop the progression of chronic venous disease?

Dr Geroulakos. Further research is required to establish whether micronized purified flavonoid fraction (MPFF) stops the progression of CVD.

Dr Kan. I recommend the use of MPFF with compression stockings to prevent the further development of CVD.

Dr Lobastov. There is no evidence that using MPFF can reduce or abolish CVD progression and varicose vein recurrence in humans. However, encouraging data were obtained from the studies with experimental venous hypertension in rats and hamsters. The first model suggested the creation of a femoral arteriovenous fistula in rats, leading to increased venous diameter, decreased valvular height, and the appearance of blood reflux on day 7 and later after surgery.[61,62] Morphological changes were accompanied by leukocyte infiltration and inflammatory response in the venous wall. At the same time, administration of MPFF resulted in a decreased leukocyte infiltration and reduced reflux rate. The second experimental model suggested ligation of an external iliac vein in hamsters, leading to chronic venous hypertension accompanied by leukocyte rolling, adhesion, and dilating of distal veins starting 6 weeks after surgery.[63] In small venules, the diameter increased immediately, reaching a maximum at 4 hours after surgery, accompanied by leukocyte adhesion, beginning simultaneously and achieving the peak at 3 days.[64] Treatment with MPFF in such cases decreased leukocyte rolling and adhesion, as well as vein diameter, measured at 6 weeks for larger vessels and at 5 days for smaller ones. Thus, treatment with MPFF allowed for increasing venous resistance against high experimental hypertension. First human trials suggest that therapy with MPFF may abolish transitional reflux in the GSV.[65] However, all these suggestions should be confirmed in robust RCTs.

Dr Josnin. In this patient, the practitioner can immediately prescribe compression and VADs. European guidelines indicate a Grade A level of recommendation: MPFF is strongly recommended for ''treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and QOL.''[29]

Conclusion

- Pregnancy is a well-established and essential risk factor for developing CVD and varicose veins in women. However, the risk of further deterioration and complications of pre-existing CVD in pregnancy is not established.
- The influence of hormonal contraception on the development and progression of CVD and varicose veins is controversial, and no clear guidelines for perioperative management exist. Based on the individual VTE risk, the decision to cease hormonal contraception and to use perioperative thromboprophylaxis should be made case by case.
- Scheduled pregnancy should not be considered as a contraindication for varicose vein surgery. However, there is no evidence of a better moment to perform an intervention before or after pregnancy, balancing the risk of complications and varicose vein recurrence.
- Modern endovenous interventions on varicose veins have no limitation by age and could be safely performed even in elderly patients receiving oral anticoagulants without their withholding.
- CVD is a steadily progressive disease that should be treated properly from the early stages. Experimental studies in animals encourage that treatment with MPFF can slow progression. However, these findings should be confirmed in well-controlled RCTs in humans.

CORRESPONDING AUTHOR

Matthieu Josnin

Clinique St Charles, 11 boulevard René Levesque, 85000 La Roche sur Yon, France

EMAIL: *matthieu.josnin@gmail.com*

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CLINICAL CASE 3.

Challenging chronic venous disease treatment within the background of comorbidities

Chung-Dann Kan, MD, PhD

Department of Surgery, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

A 51-year-old female patient visited our cardiovascular surgery outpatient clinic with a chief complaint of small, visually obvious veins in her left leg, with soreness and pain sensation noted for years.

She had no history of diabetes or hypertension. However, she had undergone splenectomy for an idiopathic thrombocytopenic purpura (ITP) state and a total abdominal hysterectomy 10 years earlier for a uterine mass and adenomyosis, complicated by pelvic adhesions the following year.

In the photo taken at her visit *(Figure 1)*, we can see that the left leg is slightly thicker than the right, and there are apparent dermatitis and telangiectasia. Outpatient vascular ultrasound showed only mild dilation of the great saphenous vein without significant deep venous thrombosis. At first, I advised her to wear compression stockings and take micronized purified flavonoid fraction. She felt slightly improved in terms of soreness but still complained of leg swelling and dermatitis. So, she underwent computed tomography venography, which showed some compression of the left iliac vein. *(Figures 2 and 3)*. I suggested that she undergo venous stent surgery; however, considering her hidden danger of ITP, she is still hesitant to have the operation. Up to this point, she has maintained her medication and lifestyle modification.

Keywords

acute coronary syndrome | anticoagulant | antithrombotic | chronic venous disease | idiopathic thrombocytopenic purpura | venous stenting

Phlebolymphology. 2023;30(2):80-83.

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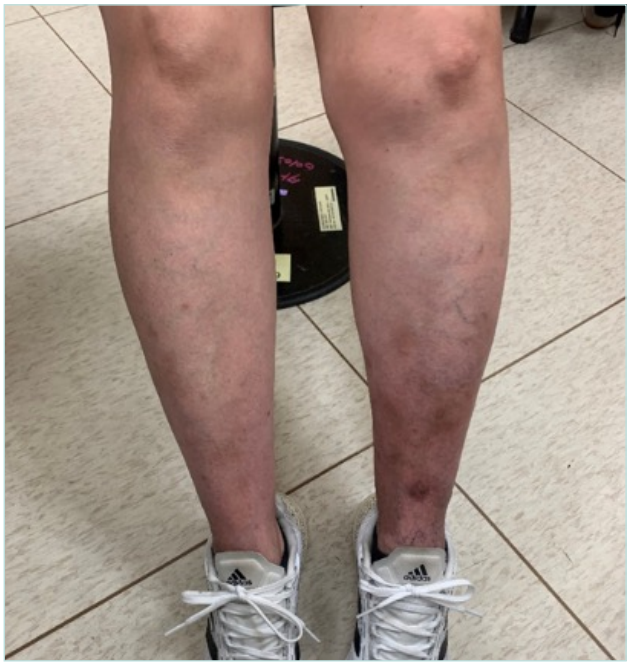

Figure 1. Clinical signs of chronic venous disease in patients. A photo taken during the medical visit shows the left calf with reticular veins, telangiectasias, and skin pigmentation in the lower third.

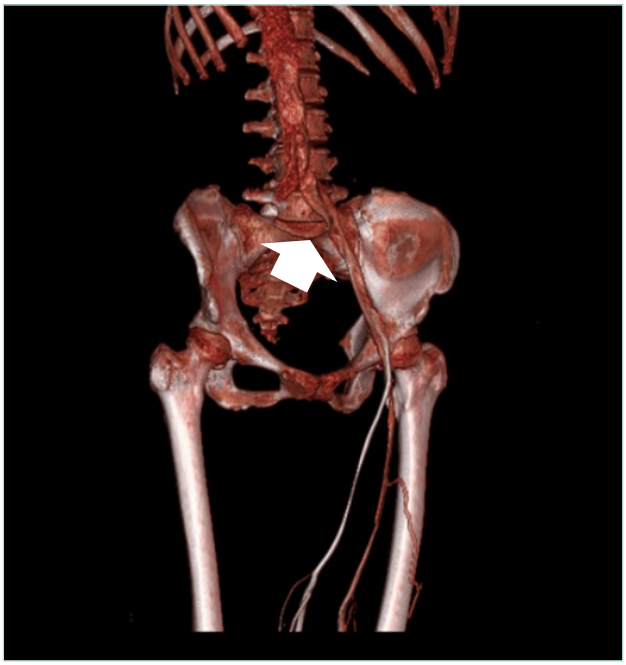

Figure 2. Results from computed tomography (CT) venography in the patient showing left-sided nonthrombotic iliac vein lesion. The lesion site is marked with a white arrow.

Discussion

Are there any limitations for venous stenting in patients with idiopathic thrombocytopenic purpura?

Dr Kan. Idiopathic thrombocytopenic purpura (ITP) is characterized by immune-mediated premature destruction of platelets, leading to thrombocytopenia and bleeding complications for patients. ITP usually manifests as hemorrhage. Paradoxically, sometimes it presents as thrombosis. Available data and evidence suggest an increased incidence of thromboembolism in patients with ITP, but the link between these two contradictory processes still needs to be studied in more detail.[1]

According to previous treatment experience of percutaneous coronary intervention (PCI) and stenting combined with dual antiplatelet drugs (DAPT) in patients with ITP complicated by acute coronary syndrome (ACS), therapy to increase platelet counts for ITP and therapy to inhibit platelet activity for ACS are somewhat contradictory, and an imbalance between them can lead to life-threatening complications.[2] Questions to be addressed for these patients include: (i) What should be the ideal minimum platelet count in treating such patients undergoing vein stenting with antithrombotic therapy? (ii) What is the ideal antiplatelet therapy for these patients? (iii) What is the mechanism of stent thrombosis in this patient? (iv) How do we avoid bleeding/thrombotic complications while maintaining adequate platelet counts and continuing antithrombotic therapy?

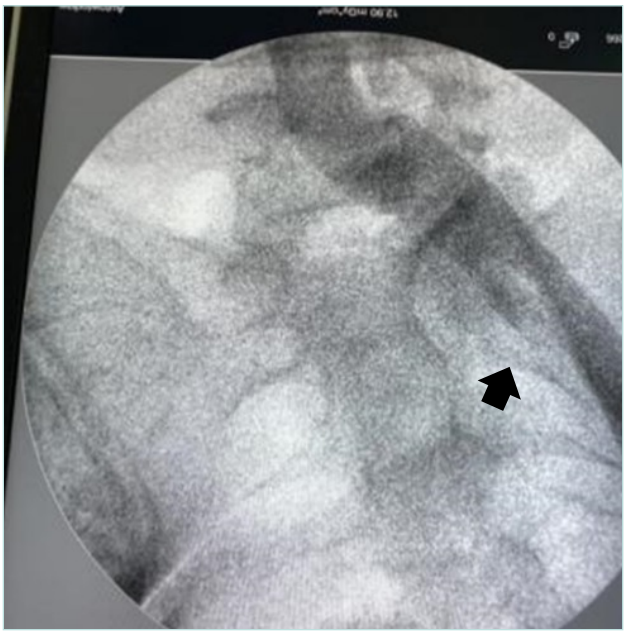

Figure 3. Venography in the patient showing a left-sided nonthrombotic iliac vein lesion. The lesion site is marked with a black arrow.

Dr Nikolov. There is no contraindication for venous stenting in patients with ITP, but I would prefer to use fondaparinux for postprocedural anticoagulation.

Dr Tazi Mezalek. There is a risk of bleeding in the case of ITP if the platelet count is below 50 x 10^9/L. If the platelet count is higher than this value, most of the procedures can be performed. The discussion will be about postprocedure anticoagulation. The symptoms of venous obstruction not being major, I propose a conservative treatment. ITP, even if in remission, may recur and interfere with chronic post-procedure anticoagulation.

Dr Lobastov. There is no direct evidence for venous stenting in the setting of ITP, and different interventions may be limited by platelet level. So, minor surgery is recommended when the platelet count is >50 x 10^9/L, whereas major surgery and epidural anesthesia require a platelet count >80 x 10^9/L.[3] After venous stenting is performed, antithrombotic therapy will be required, which may also be limited by platelet count. In the absence of direct recommendations for ITP, some suggestions from a population of patients with cancer-associated thrombosis may be stated.[4] When the platelet count is >50 x 10^9/L, full therapeutic doses of direct oral anticoagulants (DOACs) or single antiplatelet treatment (SAPT) with low-dose aspirin or clopidogrel (in the absence of other major bleeding risk factors) may be administered. When the platelet count is 25-50 x 10^9/L, DOACs should be switched to low molecular weight heparin (LMWH) in half of the therapeutic or prophylactic dose, and SAPT should be withheld. When the platelet count is <25 x 10^9/L, antithrombotic treatment should be stopped until recovery of the platelet count. Considering the increased risk of intervention and complicated postoperative management, venous stenting may be avoided in patients with ITP.

What is the best antithrombotic therapy after venous stenting, considering idiopathic thrombocytopenia?

Dr Kan. Combining antiplatelets and anticoagulants after venous stenting remains controversial. The international Delphi consensus on antithrombotic treatment after venous stenting looked at scenarios including nonthrombotic iliac vein lesion (NIVL; manifesting as May-Thurner syndrome caused by extravascular compression), residual obstruction after thrombolysis, and postthrombotic syndrome. It is recommended to treat these lesions. Recommendations reaching consensus for treatment of these lesions are as follows: i) anticoagulant therapy after stenting within 6 to 12 months (as the first choice); ii) LMWH for the first 2 to 6 weeks of treatment (this appears to be an option); iii) after multiple deep venous thrombosis (DVT) events, lifelong anticoagulation is recommended; iv) after venous stenting for 1 episode of DVT, it is suggested that anticoagulants be discontinued after 6 to 12 months. No consensus was achieved regarding the role of prolonged antiplatelet therapy.[5]

Considering idiopathic thrombocytopenia, there does not appear to be a best solution for antithrombotic therapy after venous stenting. However, in reports for those patients with ACS, some authors suggest that DAPT can be used when the platelet count is >30 x 10^9/L without bleeding. Implanting a bare metal stent to shorten the course of clopidogrel treatment is an option. In some patients with chronic asymptomatic ITP (platelets >100 x 10^9/L), no bleeding complications have been reported with drug-eluted stent implantation and DAPT. Given the lack of high-quality scientific evidence on managing these patients to support recommendations about their treatment, treatment should be individualized to minimize both risks.[6]

Dr Nikolov. The most logical antithrombotic therapy would be fondaparinux—a short duration for NIVL (2-4 weeks) and no antithrombotics afterward.

Dr Tazi Mezalek. The management of patients with both thrombocytopenia and an indication for anticoagulation is challenging. Evidence to guide appropriate treatment in this setting is very limited. Some authors have suggested that the risk of thrombosis is even higher in patients with ITP who have a distinct indication for anticoagulation, particularly after administration of ITP treatments and improvement of thrombocytopenia. The optimal approach to the use of anticoagulation in an individual with thrombocytopenia, including decisions regarding the need for anticoagulation, dosage of anticoagulant, therapies to increase platelet count, and alternatives to anticoagulation if the risk of bleeding is deemed too high, is still in question.

Dr Lobastov. Stenting of NIVL seems to be safe and effective, with primary patency of 96% at 1 year, so the need for long-term anticoagulation was critically appraised toward short-term treatment with antiplatelets.[7,8] Considering the increased bleeding risk in patients with ITP, treatment with clopidogrel for 3 to 6 months, driven by platelet count, may be justified.

Could treatment with MPFF improve skin changes in patients with chronic venous disease?

Dr Josnin. The international chronic venous disease (CVD) guidelines assign a Grade A recommendation level to the use of micronized purified flavonoid fraction (MPFF) for skin changes, and the European Society for Vascular Surgery (ESVS) guidelines have recently taken this up.[9,10]

Dr Kan. MPFF may play a role in arresting the progression of CVD. I recommend that this patient use MPFF and compression stockings to prevent her further developing CVD. She still has some swelling, with a larger-sized left leg at the moment, and I advised her to have a venous stent placed. However, the patient declined this recommendation due to concerns about her ITP disease and future risk.

Dr Tazi Mezalek. The use of venoactive drugs (VADs) is considered an essential component of the medical treatment of CVD. Based on high-quality evidence, MPFF is highly effective in improving leg symptoms, edema, and quality of life (QOL) in patients with CVD. A systematic review and meta-analysis showed the effectiveness of MPFF across the spectrum of defined venous symptoms, signs, QOL, and treatment assessment by the physician.[11] Regarding

objective assessments of leg edema, and leg redness, the use of MPFF compared with placebo reduced ankle circumference and significantly improved skin changes.

Dr Lobastov. According to the meta-analysis performed within European guidelines for CVD, MPFF is the only VAD that can affect skin changes and is strongly recommended for this purpose[9]; the number needed to treat (NNT) to achieve improvement in skin changes is only 1.6, which is very high among all VADs according to different indications. The essential question is about treatment duration. The routinely recommended course of 2 to 3 months may not be enough for patients with progressive CVD, so they may benefit from a course of therapy that is prolonged up to 6 months.[9]

Conclusion

- Venous stenting for NIVL in patients with ITP may be challenging due to the increased risk of periprocedural bleeding, so the decision to stent should be made case by case considering platelet count and its dynamic changes.
- Platelet count should drive antithrombotic management after stenting of NIVL in ITP. Single antiplatelet therapy with clopidogrel for 3 to 6 months may be suggested.
- MPFF is the only VAD that can improve skin changes in patients with CVD and is strongly recommended for this indication. The duration of the treatment course is essential, and it may be prolonged up to 6 months to achieve benefits.

CORRESPONDING AUTHOR

Chung-Dann Kan

National Cheng Kung University Hospital, 138, Sheng-Li Road, Tainan, Taiwan, R.O.C. 704

EMAIL: kcd56@mail.ncku.edu.tw

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CLINICAL CASE 4.

Chronic occlusion of inferior vena cava and pelvic venous disease

Kirill Lobastov, MD, PhD

Pirogov Russian National Research Medical University, Moscow, Russia

Anastasia Akulova, MD, PhD

Central Clinical Hospital "Railway-Medicine," Moscow, Russia

A woman, 29 years old, asked for medical attention in 2021 due to complaints of heaviness in the lower limbs, varicose veins on the left thigh, and painful menstruation. As known from her personal history, at the age of 7 months, she sustained an extensive skin burn that required skin grafting. After that, she had no complaints till 2016, when, at 24 years old, she initially noted varicose veins on the left lower limb. In 2018, at 26 years old, she underwent high ligation and stripping of the great saphenous vein (GSV) on the left side. In 2021, she noted varicose veins recurrence on the same limb and the appearance of painful menstruation that forced her to seek medical attention. She had no pregnancies and never used contraceptive pills.

Clinical examination revealed no changes in limb size, normal skin color without trophic changes, the presence of a 4-cm scar in the inguinal region on the left side, and minor spots after stab incisions on the left thigh and calf. Varicose veins without any pain and inflammation were observed on the medial aspect of the left thigh and calf and the left side of the abdominal wall. No changes were found on the right lower limb *(Figures 1 and 2)*.

A duplex ultrasound showed the absence of GSV trunk or its stump on the left thigh and a trunk with neither reflux nor dilation on the calf. The varicose veins of the limb and abdominal wall were connected with perineal veins of 2 to 4 mm in diameter that represented reflux with the Valsalva maneuver and with distal compression.

Due to painful menstruation and signs of pelvis-perineal reflux, a transvaginal ultrasound scan was performed. It revealed no pathological changes in the uterus

Keywords

gonadal vein | inferior vena cava occlusion | micronized purified flavonoid fraction | pelvic congestion syndrome | stenting | varicose vein

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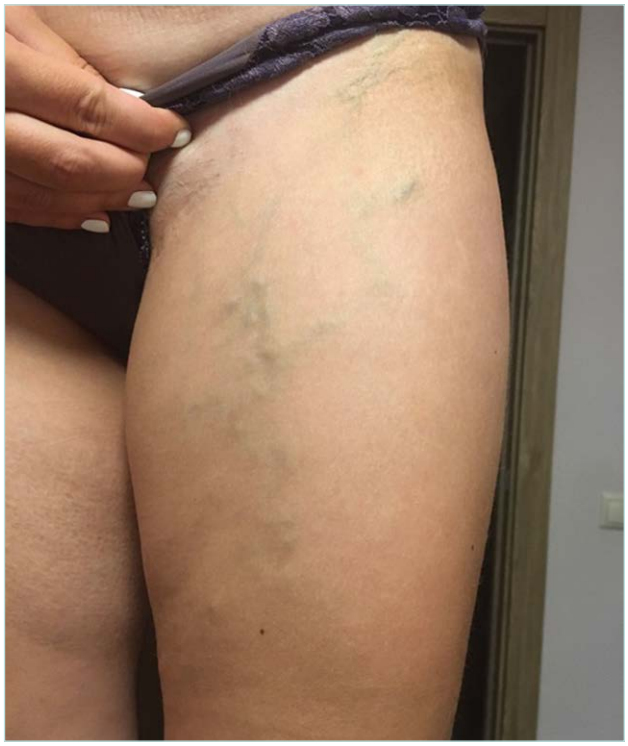

Figure 1. Left thigh with varicose veins, and a scar after high ligation in the inguinal fold.

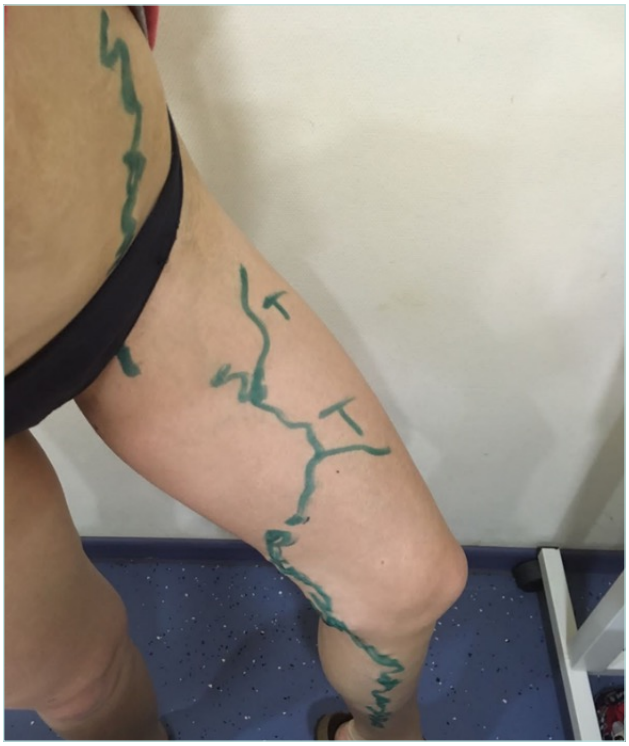

Figure 2. Marked recurrent varicose veins of the left calf, thigh, and abdominal wall.

and ovaries, whereas parametrial veins were dilated up to 13 to 15 mm with spontaneous blood contrasting. Reflux in parametrial veins was detected with the Valsalva maneuver.

The patient was referred to computed tomography (CT) venography. It found postthrombotic changes in the infrarenal, renal segment of the inferior vena cava (IVC); on the right side, common iliac vein (CIV), external iliac vein (EIV), common femoral vein (CFV) and femoral veins; and on the left side, CIV, EIV, and femoral vein. The gonadal veins (GV) were dilated up to 14 mm on the right and 19 mm on the left side. Also, anastomosis of the left GV with ascending lumbar veins was detected. The obturator veins were dilated up to 7 mm on the right and 4 mm on the left. There were observed dilated ascending lumbar veins with uneven contours, the presence of retractions, and postthrombotic intraluminal contrast defects with drainage into the system of unpaired and semi-unpaired veins *(Figures 3 and.4)*. Thus, CT venography concluded the postthrombotic obstruction of IVC and iliac veins on both sides with collateral blood flow through dilated right and left GV, lumbar veins, and obturator veins.

The final diagnosis is C2rs Esi As,d Pr (NSV, PELV) Po (IVC, CIV, IIV, EIV, CFV) LIII by CEAP (clinical, etiological, anatomical, pathophysiological) 2020 classification, and S2 V2,3b Po (IVC, BCIV, BEIV) Pr (BGV, PELV) by SVP (symptoms-varices-pathophysiology) classification.[1,2]

Discussion

Is there any indication for IVC stenting?

Dr Geroulakos. The clinical stage of the patient's recurrent venous disease is C2, and she only complains of painful menstruation. In addition, the degree of stenosis in the inferior vena cava (IVC) is not known. It is highly unlikely that symptoms will change with IVC stenting, and painful menstruation is not a recognized indication for iliocaval stenting.

Dr Josnin. My opinion for this patient would be to initially implement an optimized medical treatment, including prevention of new thrombosis, optimization of venous compression, and venoactive drug treatment. Endovenous treatment would be re-evaluated in case of ineffectiveness of these measures, taking into account the non-negligible risk of failure of the procedure and/or postprocedure recurrence and, of course, the patient's current complaints.

Dr Kan. Patients with IVC obstruction may have chronic lower-limb venous disease symptoms, experience acute deep venous thrombosis (DVT), or be restricted from physical activity.[3] Conservative treatment with anticoagulation and

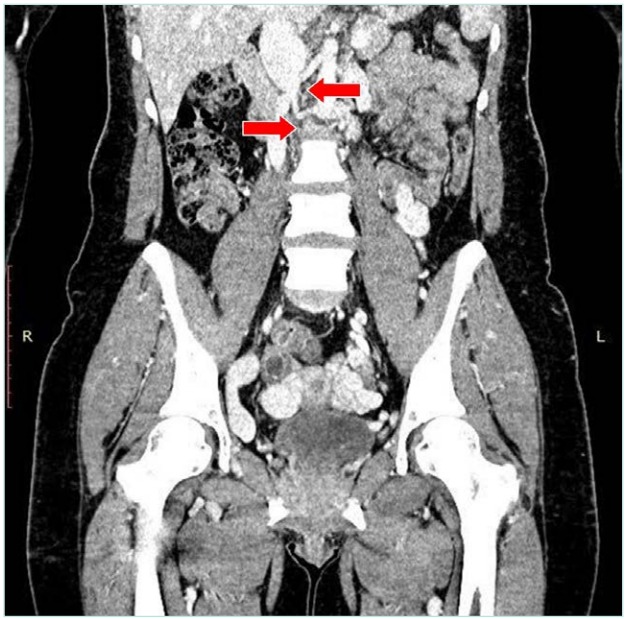

Figure 3. Computed tomography (CT) venography. Red arrows mark obstruction of infrarenal interior vena cava.

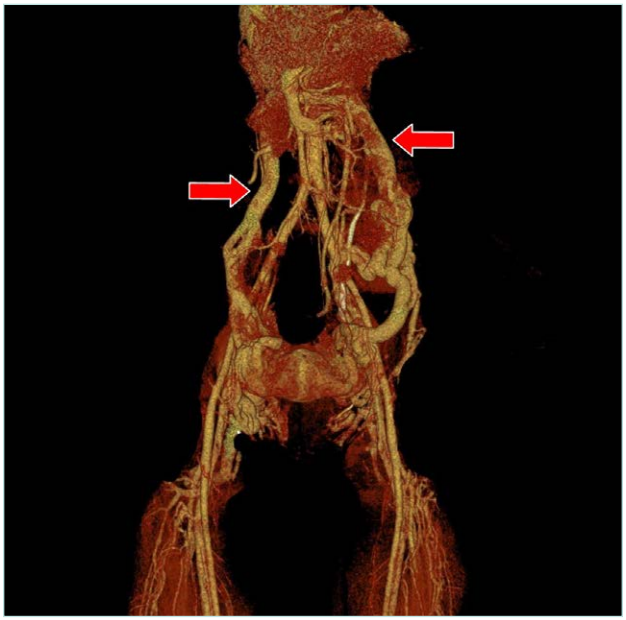

Figure 4. Computed tomography (CT) venography with 3-dimensional reconstruction. Red arrows mark dilated left and right gonadal veins.

compression therapy may provide symptomatic relief and prevent recurrent thrombosis, but a number of patients will progress. The endovascular approach with stent placement for chronic IVC obstruction is a safe treatment option to help patients without limited clinical improvement. For some problematic cases, surgical reconstruction of the IVC has been described in publications by surgical bypass.[4]

However, if we do not do endovascular procedures for these patients, there is no hope of sustained clinical improvement and possible symptom relief. According to the patient's current condition, even though the patient currently has symptoms of dysmenorrhea and a recurrence of varicose veins, there are no changes in limb size, and she has normal skin color without trophic changes. We could try to wire and connect the long-occluded iliac vein to the IVC, but this might be challenging. But we also can choose conservative treatment first because the symptom now seems to have no strong indication for IVC stenting.

Dr Nikolov. If asymptomatic (no leg edema, no skin changes), there is no indication for invasive treatment.

Dr Lobastov. Still, there is no clear consensus on the indication for interventional treatment of iliocaval venous obstruction. However, most recent guidelines suggest treating only symptomatic forms of chronic venous disease (CVD) with severe symptoms and signs, including clinical classes of C3-6 by CEAP and patients with venous claudication.[5-8] For individuals with pelvic congestion syndrome (PCS), venous stenting may be suggested for symptomatic improvement, especially if embolization of gonadal veins (GVs) is not effective.[9] Limited evidence suggests improved clinical outcomes regarding chronic pelvic pain in women with PCS, nonthrombotic iliac vein lesion (NIVL), and gonadal reflux who were stented in adjunction or instead of embolization.[10,11] However, the data on the association of PCS with IVC obstruction (particularly, agenesis) is limited, and a best treatment approach is not developed.[12,13] So, in the absence of severe symptoms of CVD and PCS, stenting should be avoided.

How effective and safe is IVC stenting?

Dr Geroulakos. IVC stenting is effective and safe in the majority of patients. An uncommon immediate complication is proximal stent migration. Intermediate complications include contralateral leg DVT secondary to the jailing of blood in unilateral iliac stents extending to the IVC and in-stent stenosis secondary to intima hyperplasia.

Dr Kan. IVC stenting is a safe procedure in this era, but the vein must be recanalized safely first. The technical success rates for iliac vein and IVC endovascular procedures—whether for nonthrombotic lesions, thrombotic lesions, or chronic postthrombotic lesions—are all high, ranging from 94% to 96%. Major bleeding complication rates range from 0.3% to 1.1%, pulmonary embolism from 0.2% to 0.9%, periprocedural mortality from 0.1% to 0.7%, and early thrombosed rates from 1.0% to 6.8%.[14]

The stenting of complex lesions involving both iliac veins and IVC is sometimes challenging. Multiple stents might be needed to recreate a bifurcation, which may lead to problems at the bifurcation when one or more stents compete and "crush" the contralateral stent. This issue may be overcome by simultaneously deploying the newer nitinol stents from both sides. A trouser configuration can also be constructed using balloon-expandable stents, as described by de Graaf et al.[15] It is essential to recreate the bifurcation slightly higher (2–3 cm) than the natural confluence to avoid excessive

angulation of the limbs (particularly the left) as they pass into the common iliac vein (CIV).

Dr Nikolov. IVC stenting is effective and safe for chronic occlusive disease with good midterm outcomes and low reintervention rates.[16]

Dr Tazi Mezalek. Venous stenting for CVD is increasingly used as more evidence supports these interventions' safety, efficacy, and durability. The evidence base for IVC stenting consists of predominantly single-center, retrospective, observational studies with a high risk of bias. Nonetheless, the procedure appears safe with few major adverse events, and studies that reported clinical outcomes demonstrate improvement in symptoms and quality of life (QOL).[17] However, no devices are currently licensed for use in the IVC, and randomized controlled trials (RCTs) or prospective registry-based studies with larger patient numbers and standardized outcomes are required to improve the evidence base for this procedure.

Dr Lobastov. The recent systematic review combining data from 33 studies reported a technical success rate of 100% (78%-100%), primary patency of 75% (38%-98%), secondary patency of 91.5% (77%-100%) with 33 major complications (3 pulmonary embolisms, 12 stent migrations, 15 major bleedings, and 3 deaths) in 1575 patients.[17] These data suggest that IVC stenting is technically effective and safe. However, the clinical efficacy and impact on QOL still need to be studied in well-controlled randomized clinical triasl (RCTs).

Is GV embolization possible in the case of IVC obstruction?

Dr Kan. Understanding the clinical and anatomical variations of the pelvic venous system plays a vital role in the diagnosis and approach to transcatheter management of pelvic varices. The essential features of the GVs are determined by venography of the IVC and pelvic vein (PELV). These features should be considered during endovascular interventions to avoid possible complications.

In the case of IVC occlusion, embolization of the enlarged GV should be done with special care, as it may be the only drainage route. In addition, whenever the GV diameter is greater than 12 mm, there is an increased risk of coil migration into the pulmonary artery, which is one of the major complications of the procedure. Other complications of GV embolization include venous perforation, local phlebitis, DVT, and reactions to the contrast agent.[18]

Dr Nikolov. Absolutely, the access would be through a jugular vein, and I would perform coil embolization and sclerotherapy. This would affect both the pelvis and the lower limb's varicose veins. PCS symptoms are more likely to disappear.

Dr Lobastov. There is no clear evidence of GV embolization's reliability, efficacy, and safety with persistent IVC occlusion. On the one hand, dilated GV may be the primary collateral for the venous outflow from the pelvis, so its occlusion may lead to the exacerbation of PCS and CVD symptoms. On the other hand, well-developed alternative collaterals (lumbar veins) may support reflux and reduce the clinical efficacy of embolization. So, the decision should be made case by case after a precise examination of individual venous anatomy of pelvic and abdominal veins. In general, treating reflux in the presence of occlusion is often not effective.

Does pelvic congestion affect fertility and outcomes of pregnancy?

Dr Dzhenina. Currently, PCS is considered one of the causes of reduced fertility in men. However, no convincing data confirm the relationship between pelvic varicosities or PCS with female infertility and increased risk of miscarriage or other pregnancy complications.[19]

Actually, this young woman managed to get pregnant and delivered by the time of this publication. Pregnancy occurred within 6 months, and pregravid preparation included folic acid 400 mcg/day and vitamin D 2000 IU/day.

At the onset of pregnancy, the venous thromboembolism (VTE) risk was assessed. Considering postthrombotic changes of pelvic and abdominal veins as a personal history of VTE, the risk of recurrent venous thrombosis was deemed high by a combination of factors. In this regard, half of a therapeutic dose of enoxaparin adjusted by prepregnancy body weight was administered for secondary VTE prevention from the early stages of pregnancy until the onset of labor. Also, the patient regularly used compression stockings of 23 to 32 mm Hg to relieve venous symptoms. There were no complications of pregnancy, bleeding, or VTE recurrences.

By the time of labor, the pregnancy was full-term, and the delivery was physiological without complications. Anticoagulation was resumed on the first day after delivery and continued for 6 weeks postpartum. No complications were observed, and breastfeeding was maintained. The child is now healthy and developing according to age.

Is treatment with MPFF indicated and effective in pelvic congestion syndrome?

Dr Geroulakos. Micronized purified flavonoid fraction (MPFF) should be considered for the management of pain and heaviness in lower limbs.

Dr Josnin. Evidence suggests that for women with PCS, conservative treatment with MPFF is associated with improved QOL and reduced symptom severity.[20,21]

Dr Kan. MPFF, a venoactive drug, has been widely investigated in PCS.[20-23] All studies demonstrated that MPFF 1000 mg daily reduced the severity of pelvic symptoms, such as pain, heaviness, and labia majora swelling secondary to pelvic varicose veins. Additionally, it was shown that a double dose of MPFF (1000 mg twice daily) in the first month of

treatment provides a quicker resolution of symptoms.[24] Interestingly, MPFF also reduces chronic pelvic pain caused by prostatitis due to increased venous return through the perineum.[25]

Dr Tazi Mezalek. Several authors suggest conservative medical management as a first-line therapy in PCS or pelvic venous insufficiency.[26] The data are limited as they come from small, randomized trials. Women treated with goserelin, medroxyprogesterone acetate, or an etonogestrel implant reported improved pain and venography scores. MPFF has been shown to decrease the severity of the clinical manifestations in some reports of pelvic varicose veins. Patients who do not respond to medical therapy can pursue invasive treatment, embolization being the gold standard in treating those cases.

Dr Lobastov. Chronic pelvic pain is the most common symptom of PCS.[27,28] The true origin of it is still under investigation. However, several neurobiological factors have been discovered, including calcitonin gene-related peptide and substance P.[29-31] Among all conservative approaches, MPFF demonstrated high clinical efficacy in reducing chronic pelvic pain and pain syndrome after embolization.[26,32] So, using MPFF is advocated to improve PCS symptoms and relieve CVD symptoms.

What treatment option is preferable for varicose veins of lower limbs?

Dr Geroulakos. In this scenario, foam sclerotherapy is the preferred treatment option for recurrent varicose veins.

Dr Josnin. Before anything else, a complete exploration of the deep venous network is essential. I would perform a magnetic resonance venography (MRV) and then, if possible, treat with endovenous laser and phlebectomy if necessary. I would not do sclerotherapy in this patient because of the thrombotic risk.

Dr Kan. To treat varicose veins with some swelling in the lower extremities, I would first do CT venography or MRV to understand the anatomy of the entire vein and determine the best treatment strategy for the patient. If the varicose veins are related to the saphenous trunk problem, I would do endovenous ablation or surgical ligation and stripping. If the only lesion is limited to superficial veins, I would do a local phlebectomy or sclerotherapy.

Dr Nikolov. For that particular case, the preferable treatment option would first be embolization of both GVs and sclerotherapy or miniphlebectomy for lower-limb varicose veins.

Dr Tazi Mezalek. Varicose veins are dilated, twisty veins close to the skin's surface that usually occur in the legs, caused by chronic venous insufficiency. Varicose veins can be painful, itchy, and unsightly, especially when standing and walking. Occasionally, they may result in complications like ulcers on the leg. Traditionally, surgery was used to remove the pathological vein. Several treatments have emerged using endovenous laser ablation therapy (EVLT), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (UGFS), or cyanoacrylate embolization (CAE). Still, heat-based endovenous therapy with a laser may be more effective than traditional surgery and can effectively prevent the recurrence of varicose veins in the longer term.

Dr Lobastov. Considering complete removal of the GSV trunk without any stump with the previous open surgery and connection between thigh and perineal veins, UGFS and ambulatory phlebectomy to remove recurrent varicose veins are methods of choice. Also, local procedures for varicose veins and related pelvic escape points are recommended for patients with varicose veins of pelvic origin.[8] In practice, considering the gentle skin of the perineal zone and attempts to close escape points, UGFS may be preferable. However, it is essential to discuss with the patient the risk of further progression of pelvic venous disease and early recurrence of varicose veins in the presence of untreated iliocaval obstruction and GV reflux.

Conclusion

- Obstruction of IVC is a rare but known reason for the development of pelvic congestion syndrome.
- IVC stenting is a well-established intervention with good technical outcomes and a low rate of complications but is often challenging and resource consuming. It is indicated in patients with severe symptoms and signs of CVD. Venous stenting to improve symptoms of PCS is under debate.
- The decision to embolize GVs in the presence of untreated IVC obstruction should be discussed case by case after the precise evaluation of the anatomy of the pelvis and abdominal veins. The primary role of GV in venous outflow from the pelvis should be excluded to avoid the exacerbation of PCS and CVD.
- There is no clear evidence that PCS affects fertility or pregnancy outcomes in women.
- MPFF effectively reduces pelvic pain associated with PCS. It could be used in patients with pelvic venous insufficiency to control symptoms of CVD and PCS.
- UGFS and ambulatory phlebectomy could be used to remove varicose veins of pelvic origin. However, the risk of further progression of PCS and varicose veins recurrence in the presence of pelvic venous insufficiency has not been estimated.

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CORRESPONDING AUTHOR

Kirill Lobastov

Department of General Surgery, Pirogov Russian National Research Medical University, Ostrovitianova str. 1, Moscow, 117997, Russian Federation

EMAIL: *lobastov_kv@hotmail.com*

CLINICAL CASE 5.

Timing of superficial and deep vein endovascular interventions for the treatment of venous leg ulcers

Nadelin Nikolov, MD, PhD

Department of Vascular Surgery, National Heart Hospital, Sofia, Bulgaria

We present a case of a 66-year-old female with a recurrent venous leg ulcer (VLU) in the left medial malleolus. The patient had suffered iliofemoral deep venous thrombosis (DVT) 10 years ago. She was treated with oral anticoagulation for 2 years and venoactive drugs but no compression stockings. Since then, she has complained of visible varicose veins, swelling, and discomfort in her left leg. Five years after the index DVT, she developed a small VLU in the area of the left medial malleolus, which became bigger over time. The ulcer was treated with various kinds of dressings but never healed completely.

We performed duplex ultrasound and found concomitant vein pathology: both reflux and obstruction. The great saphenous vein (GSV) was 9 mm in diameter with reflux. Also, chronic occlusion of the left common iliac vein was detected.

Our treatment plan was to intervene in both pathologies. First, we performed radiofrequency ablation of the GSV trunk from the calf's middle third. After the procedure, we added a knee-length compression stocking with a pressure of 30 to 40 mm Hg at the ankle. One week later, we performed endovascular intervention of the deep veins. Under ultrasound guidance, we punctured the left common femoral vein. Left common iliac vein occlusion was verified and crossed

Keywords

anticoagulant | iliac vein obstruction | micronized purified flavonoid fraction | superficial venous reflux | venous leg ulcer | venous stenting

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with a stiff hydrophilic guidewire supported by a Berenstein catheter. Predilatation with a 10-mm balloon catheter and afterward dilatation with a 14-mm noncompliant balloon was performed. We used intravascular ultrasound (IVUS) to determine the length of the occlusion and external iliac vein diameter. It was found to be 11 mm, so we decided to implant a 14/90-mm Wallstent. After the postdilatation with a 14-mm balloon, we noted brisk flow in the inferior vena cava and disappearing of the collaterals. The patient was discharged on prolonged antithrombotic, venoactive drug, and compression therapy the next day. We achieved complete ulcer healing after 1 month.

Discussion

How does the presence of iliac vein obstruction impact venous ulcer healing?

Dr Geroulakos. The presence of iliac vein obstruction decreases the healing rate of venous leg ulcers (VLUs) treated with compression and superficial venous reflux elimination and increases the recurrence rate. Raju S et al have reported cumulative rates of limbs with healed ulcers and freedom of ulcer recurrence in legs with healed ulcers (C5) at 5 years to be 54% and 88%, respectively.[1]

Dr Kan. VLUs account for 70% to 80% of ulcers assessed and treated in clinics, with a prevalence of up to 2% of the population. VLU healing involves coordinated processes, including hemostasis, inflammation, proliferation, and remodeling, and the contribution of different cells, including leukocytes, platelets, fibroblasts, vascular smooth muscle cells, endothelial cells, and keratinocytes, as well as the release of various biomolecules, including transforming growth factor, cytokines, chemokines, matrix metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), elastase, urokinase plasminogen activator, fibrin, collagen, and albumin. With good wound care and compression therapy, VLU usually heals within 6 months.[2]

The combination of chronic iliocaval obstruction and VLUs in patients can be very complex and a barrier to healing. As shown by Ruiz CS et al, patients with successful venous stent placement had significantly higher wound healing rates at 12 months than the persistent occlusion group (79.3% vs 22.6%; $P<0.001$).[3] Venous stent intervention is recommended to promote wound healing.

Patients with VLU should be evaluated for venous outflow obstruction; if present, restoration of blood flow with stent placement may improve wound healing. After venous intervention and stenting to remove the obstruction, healing time is shortened, and ulcer-free time is increased.[3]

Dr Josnin. Restoring a harmonious venous flow associated with venous compression guarantees effective healing and reduced ulcer recurrence. To my knowledge, the study by Ruiz CS et al is the one that best demonstrates this.[3]

Dr Lobastov. The prevalence of nonthrombotic and postthrombotic iliocaval obstruction of >50% in patients with active or healed VLU has been reported as 28% to 37%, whereas more severe obstruction of >80% was found in 23%.[4,5] In another study, the combination of iliocaval obstruction of >50% and superficial venous reflux was found in 32% of C5-6 patients.[6] The presence of venous obstruction may delay ulcer healing and make it recalcitrant to standard conservative treatment even after ablation of superficial reflux.[3,7-9]

Dr Nikolov. VLUs are a widespread, debilitating problem with high recurrence rates. First-line conservative treatment with graduated compression stockings is not always enough and has a high recurrence rate. Current guidelines for treating chronic venous disease recommend compression therapy and eradication of superficial reflux. Still, the pathophysiological mechanism seems to be more complex, especially in the presence of deep vein pathology.[10] We do not have clear guidelines for treating reflux and obstruction patients. Which intervention should be first? Should we treat and wait? Should we perform a staged or concomitant procedure?

How effective is venous stenting in the presence of superficial venous reflux?

Dr Lobastov. According to the systematic reviews, venous stenting is associated with ulcer healing in 73% to 80% of patients with postthrombotic obstruction, irrespective of superficial reflux.[11-13] Individual studies show that adjunctive ablation of superficial veins does not improve outcomes of venous stenting, including ulcer healing.[14,15] Others suggest that intervention on superficial veins in addition to venous stenting may improve outcomes in C4-6 patients.[16] However, all these trials are nonrandomized and do not allow the drawing of any strong conclusion.

Dr Nikolov. Venous ulcers are caused by a complex cascade of events initiated by venous hypertension resulting from venous reflux, venous obstruction, or both. When we have mixed pathology, it is not clear which to treat first or whether we have to treat both. There is evidence in both directions. Some researchers present data suggesting that correction of iliac vein obstruction dramatically improves superficial reflux.[17,18] Nowadays, there is no doubt that deep vein stenting is the first-line treatment for iliac vein obstruction (thrombotic and nonthrombotic lesions) that proves to be safe and effective. Furthermore, it is more cost-effective than standard medical and compression therapy alone.[19] It is the same for the ablation techniques for treating superficial reflux. My practice in patients who present with VLU and

superficial reflux is to correct it first with wound care and compression therapy. Despite this complex care, up to 32% do not heal, and the reason for that, in most cases, is unaddressed iliac vein obstruction.[8]

Is ablation of superficial reflux effective and safe in the presence of iliac vein obstruction?

Dr Geroulakos. In most patients, ablation of the superficial venous reflux is safe in the presence of iliac vein obstruction.

Dr Josnin. The treatment of superficial venous reflux remains safe and effective as long as the treated segment is not vicarious. Any indication for treatment in these patients must therefore make the practitioner pay particular attention to the deep venous network and the causes that led to this venous thrombosis, which may impact the type of treatment that would be chosen.

Dr Kan. The development of deep venous segmental reflux may occur primarily or may result from damage to the valves by the thrombotic process. In general, two-thirds of patients may develop valvular insufficiency 1 year after their deep venous thrombosis (DVT) events. Iliofemoral DVT and May-Thurner syndrome can lead to deep venous reflux, which then delivers hydrostatic pressure peripherally, possibly leading to clinically significant superficial venous reflux. These central venous lesions and reflux may exacerbate superficial venous insufficiency in patients with chronic venous insufficiency (CVI). When asking about superficial venous reflux, presentations of deep venous reflux are common and may be a sign of more severe CVI.[20] How to properly treat these patients is an important issue.

The retrospective cohort study by Li et al may provide clues in answering whether superficial reflux ablation is effective and safe in the presence of iliac vein obstruction. Their results showed that superficial vein surgery was safe and effective in patients with deep venous reflux, improving clinical and patient-reported outcomes compared with patients without deep vein reflux. Furthermore, they highlight that patients with and without deep vein reflux significantly improved their clinical scores and patient-reported outcomes after superficial vein treatment.[20] Deep vein reflux alone is not associated with poorer outcomes after superficial vein treatment and should not prevent intervention.

Dr Nikolov. The next big question is which pathology to treat first—reflux or obstruction. Although superficial vein ablation is the recommended treatment for reflux, there are no randomized controlled trials (RCTs) for using it in the setting of deep vein obstruction. Most physicians would say removing reflux means eliminating a potentially significant collateral network. It is, however, known that the involvement of the saphenous vein in collateral compensation of outflow obstruction will be relatively minor.[21-23] A recent systematic review by Benfor et al found that the available data are limited but suggests that ablation of superficial vein reflux is safe in patients with proximal deep vein obstruction.[24] They also found that combining ablation with stenting further improves venous ulcer healing.

Dr Lobastov. A recent systematic review addressed the question of superficial vein ablation in the presence of deep vein obstruction and concluded that it may be safe.[24] Authors combined studies with nonthrombotic and postthrombotic venous obstructions predominantly of proximal localization. In fact, only one trial by Raju S et al assessed saphenous stripping in the presence of infrainguinal obstruction, which was supplemented by the repair of deep venous valves in 81%.[25] Authors found clinical and functional improvement in all patients irrespective of deep vein status. All other studies dealt with patients having iliocaval obstruction and investigated superficial ablation and stenting in different combinations and sequences. So, it is possible to conclude the safety of superficial venous ablation in proximal deep vein obstruction when saphenous veins and their tributaries rarely provide collateral outflow. Moreover, even in the presence of a suprapubic bypass through an epigastric vein, great saphenous vein (GSV) could be easily ablated with preservations of collaterals. In contrast, data on superficial vein ablation in the presence of infrainguinal deep vein obstruction, when saphenous veins could provide significant collateral outflow, is limited. With regard to the efficacy of superficial vein ablation in the presence of proximal deep vein obstruction, the results of analyzed studies are conflicting. However, adjunctive venous stenting seems to improve outcomes of superficial vein ablation but not vice versa.[7,14,15,26]

In terms of VLU healing, individual RCTs that enrolled a limited number of patients with previous DVT (7%-9%), without deep vein obstruction, and with deep vein reflux in 32% to 38% showed an increased chance for ulcer healing and decreased risk of ulcer recurrence when ablation of superficial reflux by open surgery (ESCHAR study [Effect of Surgery and Compression on Healing And Recurrence]) for endovenous interventions (EVRA study [Early Venous Reflux Ablation]) supplemented standard conservative care.[27,28] However, due to the exclusion of patients with deep venous obstruction, these results could not be extrapolated to the current clinical case.

What surgical approach is better in patients with combined superficial and deep pathology?

Dr Geroulakos. In the absence of active or healed leg ulcers, dealing with superficial venous reflux with endovenous thermal ablation and phlebectomy may be sufficient for the management of the patient.

Dr Josnin. I have no experience in this regard, and it would seem to me that performing both procedures simultaneously would be an entirely feasible option unless reflux is suspected to have a more significant impact on ulceration. In such case, given the need for anticoagulation after stenting and a more cumbersome procedure, I would leave open the possibility of an evaluation that includes ulcer healing, the severity of venous disease, and quality of life (QOL) prior to performing the recanalization.

Dr Kan. Stent-first, ablation-first, or simultaneous surgery may be surgical options for patients with both superficial and deep venous diseases. According to the findings of Alsheekh A et al, there appears to be no significant difference, so it's unclear whether vein ablation or stenting should be performed first.[29] Also, about 16% of patients in that study said neither approach helped. I prefer to do the stent or simultaneous procedures to avoid dirty wound contamination issues.

Dr Lobastov. The current evidence does not clarify what to do first in patients with proximal venous obstruction and superficial reflux: stenting or ablation. The decision may be based on the preferences of the patient and physician, institutional capacity, and clinical features. In any case, if the first approach did not lead to ulcer healing, the second one should be utilized. However, another question can arise: if the first approach was effective, is it necessary to make a supplementary treatment? Further robust RCTs should be focused on these questions.

Dr Nikolov. A large study by Lawrence et al looked at the impact of the 3 treatment modalities on venous ulcer healing: superficial vein ablation, perforator vein ablation, and deep venous stenting.[15] Data came from 11 centers in the USA and included 832 patients. The main findings of this study are that ablation of truncal and perforating vein reflux, as well as stenting of deep vein obstruction, all contribute to the healing of venous ulceration. Patients with chronic venous ulcers should have truncal and perforator reflux treated to improve wound healing. Furthermore, patients who fail to heal with superficial and perforator vein ablation should undergo an examination of the iliocaval veins. Significant deep venous obstruction, as well as incompetent truncal veins, should be treated to improve and accelerate wound healing. It is noteworthy that patients who underwent deep venous stenting heal faster than those with untreated deep vein obstruction.

We look forward to the results from another interesting study—the DEVELOP trial (DEep VEin Lesion OPtimization).[30] Patients will be randomized to undergo either truncal ablation and compression therapy or truncal ablation, simultaneous with iliac interrogation with IVUS and stenting of significant (>50%) iliac vein lesions plus compression therapy. The primary feasibility outcome will be the rate of eligible patient participation, whereas the primary clinical outcomes will be ulcer healing and procedural safety.

In summary, our treatment strategy and preference in patients with complex pathology (both reflux and obstruction) are staged procedures. First, we correct the reflux, and there are several reasons for that. Ablation is faster and easier and is a safe intervention and can be done in an outpatient setting. Another reason is that if we perform stenting first, we should leave the patient on prolonged anticoagulation. There is much evidence that ablation in patients on anticoagulation is safe, but if we could minimize the risk of bleeding complications, we should do so.[31,32] Venous stenting is safe and cost-effective but requires much more skill and resources.

What antithrombotic regimen is preferable after stenting of postthrombotic iliac vein obstruction?

Dr Geroulakos. According to the International Delphi consensus, anticoagulation is the preferred treatment for a compressive iliac vein lesion during the first 6 to 12 months after venous stenting. Low molecular weight heparin (LMWH) is the antithrombotic agent of choice during the first 2 to 6 weeks. Lifelong anticoagulation is recommended after multiple DVTs. Discontinuation of anticoagulation after 6 to 12 months is advised after venous stenting for a single acute DVT. There is no consensus regarding the role of long-term antiplatelet therapy.[33]

Dr Kan. In comparison with bypass surgery, endovascular therapy in patients with chronic outflow obstruction is considered a good option for symptom control owing to its relative simplicity, low risk, and its being a day surgery, as conservative compression therapy may fail later. In this era of increasing use of deep vein stenting, there is currently no consensus on postoperative antithrombotic therapy regarding the duration and type of anticoagulation after chronic recanalization. However, as a general rule, thrombotic venous disease requires more aggressive medical management after surgery than a nonthrombotic disease because of the higher rate of rethrombosis in the former.

A typical treatment regimen will include an enoxaparin bridge to warfarin. Practitioners increasingly consider the direct oral anticoagulants (DOACs; rivaroxaban) as an alternative to warfarin; however, data on its efficacy after recanalization and stenting are scarce. Furthermore, patient adherence to oral anticoagulants is critical during postoperative care to avoid significant skipping of medications. Many practitioners use antiplatelet drugs such as aspirin and clopidogrel after venous stent placement, but this practice is based on arterial data and physiology.

Dr Lobastov. Stenting of postthrombotic venous obstruction is associated with the lowest primary and secondary patency compared with nonthrombotic lesions and DVT.[13,34] The reason for stent occlusion include mechanical, clinical, and therapeutic factors.[35] The recent systematic review revealed a high heterogeneity of different antithrombotic approaches that did not affect stent patency.[36] The type and duration of therapy seem to depend on the characteristics of the primary thrombotic event and the severity of venous obstruction. In postthrombotic lesions, prolonged anticoagulation is usually indicated and sometimes in combination with antiplatelets, especially in recurrent DVT and after reinterventions.[33] In case of total and extended postthrombotic occlusion, initial therapy with LMWH may be beneficial.[37] Compared with vitamin K antagonist (VKA), rivaroxaban appeared more effective after stenting postthrombotic obstructions, regarding primary patency, in-stent stenosis, symptom recurrence, and ulcer healing.[38]

So, treatment after stenting of postthrombotic deep venous obstruction therapy with LMWH for 2 to 6 weeks, followed

by rivaroxaban for 6 to 12 months with a further decision about prolonged anticoagulation made on an individual basis, is advocated. Anticoagulation for an indefinite period may be suggested for all patients except those with index DVT provoked by major transient risk factors.[39-41] Additional use of antiplatelets may be suggested after reinterventions in individuals with low bleeding risk.

Could treatment with MPFF improve venous ulcer healing?

Dr Geroulakos. Micronized purified flavonoid fraction (MPFF) counteracts the pathophysiologic mechanisms of chronic venous disease (CVD) and ulceration and has proven to be an effective adjunct to compression therapy in patients with large and chronic VLUs.

Dr Josnin. In international guidelines, MPFF has a special place in the treatment of ulcers. It was recommended in 2011 by the Society for Vascular Surgery and the American Venous Forum and in 2015 by the European Society for Vascular Surgery (ESVS) for use in healing primary venous ulcers as an adjunct to compression therapy (Class IIa, level A). Then, in 2018, it was recommended by the International Union of Phlebology and the International Union of Angiology (Grade A) and in 2022, by the ESVS (class IIa, level A).[10,42-44]

Dr Kan. MPFF has the ability to improve venous tone and capillary permeability, but the exact mechanism of action of the drug remains unclear. MPFF has anti-inflammatory, antioxidant, and powerful free-radical scavenging properties. MPFF decreases the expression of adhesion molecules by neutrophils and monocytes in patients with CVD. Based on the experimental results, MPFF usage in chronic venous hypertension prevented capillary rarefaction and the venous inflammatory cascade initiation.[45]

From the perspective of the mechanism of action, it would appear that MPFF treatment can promote the healing of venous ulcers. However, its role may be limited to adjuvant therapy. To treat venous ulcer wounds, it is still necessary to eradicate the cause, improve the lifestyle, and assist with compression therapy.

Dr Tazi Mezalek. VLU is the final stage of CVI and is the most common leg ulcer type. The ulcers are often painful and exudative, and the recurrence rates can reach 56%, especially in those who are not adherent to compression stocking therapy.[46] This cycle of healing and recurrence considerably impacts individuals' health and QOL, health care, and socioeconomic costs. Low-stretch compression is the primary treatment for VLU, which assists by reducing venous hypertension and peripheral edema and enhancing venous return. However, studies show that issues with adherence to compression therapy may be the principal cause of healing failure. Pharmacological treatment that suppresses inflammation would be an invaluable intervention to complement compression treatments. MPFF has venotonic properties and acts on leukocytes and endothelium, which results in decreased inflammation and permeability. A meta-analysis of randomized prospective studies found that MPFF accelerated the healing of leg ulcers.[47]

Dr Lobastov. According to the latest Cochrane meta-analysis, venoactive drugs (VADs) may have little or no effect on ulcer healing (risk ratio [RR] 0.94; 95% CI, 0.79-1.13).[48] However, the authors of this report combined data on different drugs, including rutosides, hidrosmine and diosmine, without separation of MPFF, aminaftone, and calcium dobesilate. The recent umbrella review found 3 systematic reviews, including the above mentioned, suggesting the efficacy of MPFF (RR, 1.36; 95% CI, 1.07-1.74) and rutosides (RR, 1.7; 95% CI, 1.24-2.34) in addition to standard compression and topical therapy for ulcer healing.[49] The individual meta-analysis of 5 RCTs with MPFF use in addition to standard compression therapy and local care found a significant 32% (95% CI, 3%-70%) increase in chance for ulcer healing and a 5-week reduction in time to heal.[47] It is important that the treatment course duration in all trials was 6 months. It could sometimes be prolonged for 12 months without increasing the risk of adverse events but with further reduced symptoms.[50] So, treatment duration with MPFF is essential to achieve individual benefit.

Conclusion

- In patients with VLUs, nonthrombotic and postthrombotic iliocaval venous obstruction is prevalent and often associated with superficial venous reflux.
- In patients with a combination of deep venous obstruction and superficial venous reflux, venous stenting and superficial ablation are often indicated together. There is conflicting evidence that superficial reflux ablation in the presence of deep venous obstruction is safe and effective or can improve outcomes in adjunct with venous stenting.
- The decision to perform ablation and stenting and the sequence of interventions should be made on an individual basis considering the preferences of the patient and physician and institutional capacities.
- After stenting of postthrombotic venous obstruction, prolonged anticoagulation with LMWH switched to DOACs is indicated for 6 to 12 months or longer after individual assessment of risks and benefits considering the nature of primary DVT, technical aspects of venous stenting,

and individual bleeding risk. Additional antiplatelet therapy may be suggested in recurrent DVT and after reinterventions.

- MPFF can improve venous ulcer healing in addition to standard conservative treatment. The duration of the therapy with MPFF of ≥6 months is essential to achieve maximal benefits.

CORRESPONDING AUTHOR

Nadelin Nikolov

Department of Vascular Surgery and Angiology, National Heart Hospital Ulitsa Konyovitsa 65, 1309 Sofia, Bulgaria

EMAIL: *nadelin.nikolov@gmail.com*

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CLINICAL CASE 6.

Prevention of postthrombotic syndrome after proximal DVT

Zoubida Tazi Mezalek, MD, PhD

Department of Clinical Hematology, Internal Medicine, Mohammed V University, Ibn Sina Hospital, Rabat, Morocco

A 38-year-old female patient, a nurse in a hospital ward, presented 6 months earlier with extensive iliofemoral deep venous thrombosis (DVT) of the right lower limb.

She was treated with rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily. The DVT remained unexplained by a classical risk factor. She has not had any surgery or hospitalization and has not traveled recently. She has 2 children aged 9 and 4 years. She has been on oral hormonal contraception for about 10 years and is currently wearing an intrauterine device since the birth of her last child. She reports no notable personal history other than some heaviness in her legs at the end of hard workdays. Her family history includes a mother and an aunt who were treated for varicose veins in the lower extremities. At the time of her current visit, she had mild diameter asymmetry in both legs, with some superficial varicosities in the right leg. The internist decided to maintain the anticoagulant treatment with rivaroxaban 10 mg once daily for an indefinite period, given the unprovoked nature of the DVT and the diagnosis of an obvious postthrombotic syndrome, especially since the patient tolerates rivaroxaban well (some increase in menstrual bleeding without consequences). He also advised her to continue wearing compression stockings and prescribed a micronized purified flavonoid fraction course.

Keywords

anticoagulants | deep venous thrombosis | postthrombotic syndrome | prevention | treatment

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Discussion

What is postthrombotic syndrome, and how common is it?

Dr Geroulakos. The transatlantic interdisciplinary consensus document defines postthrombotic syndrome (PTS) as "chronic venous symptoms and/or signs secondary to deep venous thrombosis (DVT) and its sequelae."[1] The incidence depends on the location and extension of DVT. The most common instrument for assessing the severity of PTS is the Villalta scale, which combines general symptoms and signs of chronic venous disease (CVD). My group has shown that, surprisingly, there is no relationship between the symptom and the sign part of the Villalta scale. There was an expectation that legs that were severely affected would have more symptoms, but this was not the case.[2]

Dr Josnin. PTS corresponds to chronic manifestations of secondary chronic venous insufficiency (CVI) following DVT, and PTS is the most frequent complication of DVT. Severe forms affect about 5% to 10% of patients, whereas 20% to 50% of patients are affected after a DVT, despite adapted and well-monitored anticoagulation.[3]

Dr Kan. PTS, a common and sometimes disabling complication of DVT, reduces the quality of life (QOL) and is costly, burdensome, and potentially debilitating. The manifestations of PTS range from mild clinical symptoms or signs to more severe manifestations such as chronic leg pain, intractable edema, and venous leg ulcer (VLU) that limit activity and work capacity.[4]

Dr Tazi Mezalek. PTS is the most common complication of DVT. Despite conventional anticoagulation therapy and even after the resolution of DVT, around 60% to 80% of the vein will be recanalized over months, and residual thrombus may persist.[5-7] Indeed, DVT can cause direct damage to the venous wall and associated valves. Because the lysis may not be complete in some cases, the thrombus is replaced by fibrous tissue, which may lead to functional obstruction, permanent valve alterations, and venous reflux.[8,9] These phenomena are accompanied by local inflammation that aggravates the valve lesions, but also systemic inflammation that may explain the valvular lesions also observed at a distance from the DVT in unaffected venous sites.[10,11]

PTS is therefore considered a secondary CVI. It refers to chronic clinical manifestations of venous insufficiency, ranging from mild symptoms such as mild pain, swelling, and hyperpigmentation, to more severe manifestations such as intractable pain, venous claudication, and leg ulceration. Symptoms of PTS usually occur within 3 to 6 months after DVT but can occur up to 2 years.[5-7]

The reported prevalence of PTS differs considerably among studies because of differences in the study populations, the tools used to assess PTS, and the time interval after the index DVT. Standardizing PTS assessment tools and developing patient self-assessment scales were important in researching the epidemiology of PTS, allowing comparison between studies, performing meta-analyses, and increasing the feasibility of longer follow-ups of patients with DVT. Therefore, recommendations for standardization of the definition of PTS for clinical studies have been published.[12] The International Society on Thrombosis and Haemostasis (ISTH) has adopted the Villalta scale as a standard to diagnose and grade the severity of PTS in clinical studies.[13] It has been shown to be valid, reproducible, and easy to administer.[14] Venous thromboembolism (VTE) is a growing public health problem due to increased life expectancy, an increasing proportion of elderly individuals, and an expected increase in the prevalence of PTS. Therefore, improved prevention and treatment of DVT are critical in decreasing the incidence of PTS.[3,15]

PTS is the primary determinant of patient QOL after DVT. Studies have shown that PTS harms patient QOL compared with DVT patients without PTS, either using generic measures (36-item Short Form Survey [SF-36]) or disease-specific scales (Venous Insufficiency Epidemiological and Economic Study-QOL (VEINES-QOL).[16,17] Also, PTS is a costly condition with a total cost over a 2-year period that is 2-fold higher than for DVT patients without PTS.[18] This is attributable to the greater use of health care visits and medications and the high cost of treating venous ulcers.

Dr Lobastov. Although the Villalta scale is generally validated and approved for PTS verification and severity assessment, it has a very low specificity.[19,20] It contains nonspecific symptoms and signs, which could be attributed to either primary or secondary CVD. So, if a patient had primary venous disease with a Villalta scale score ≥5 before DVT, then at 3 to 6 months after thrombosis, he must be classified as having PTS, even without exacerbation of primary CVD. The Villalta scale does not allow differentiation between preexisting symptoms of primary CVD and new symptoms of PTS. Several approaches were introduced to improve the specificity of Villalta scale, particularly adjusting on contralateral CVD, but all failed.[21] It has also been shown that Villalta scale does not capture the typical PTS complaints or their importance to patients, which is why it poorly correlates with QOL.[22] A patient-reported Villalta scale was developed and externally validated but demonstrated only moderate agreement with the original instrument.[23,24] As an alternative to the Villalta scale, the criteria of Ginsberg and Brandjes were introduced but not widely adopted.[3]
The prevalence of PTS in the population is not studied well. One epidemiological study from Russia reported PTS in 1.4% of 703 rural community residents.[25]

What are the risk factors of PTS?

Dr Geroulakos. According to a recent retrospective study, when DVT is treated using interventional methods, lower

Villalta scores are detected after 1 year of follow-up. The development of PTS is reduced substantially. According to VEINES-QOL/Symptoms scale, QOL is higher in patients who underwent interventional procedures. In short and medium terms, the interventional treatment provides persistent benefits, especially in DVT with proximal involvement.[26]

Dr Josnin. The main risk factors are the location of the venous thrombosis (the more proximal, the more severe the PTS) and a history of ipsilateral recurrent DVT. In the REVERSE study (REcurrent VEnous thromboembolism Risk Stratification Evaluation), which investigated risk factors for PTS in patients with a first episode of unprovoked proximal DVT without primary venous insufficiency, other risk factors were highlighted—obesity, poor quality of anticoagulant therapy, and residual venous obstruction.[27]

Dr Kan. The main risk factors for PTS were anatomically widespread DVT, recurrent ipsilateral DVT, persistent leg symptoms 1 month after acute DVT, obesity, and older age. PTS is thought to develop after DVT due to venous hypertension (ie, increased pressure in the veins). Venous hypertension reduces calf muscle perfusion, increases tissue permeability, and promotes the associated clinical manifestations of PTS. Two pathological mechanisms lead to venous hypertension: persistent (acute, then residual) venous obstruction and valvular incompetence due to venous valve damage.[28]

Dr Nikolov. Risk factors are proximal DVT, preexisting venous insufficiency, obesity, age, the severity of symptoms, residual venous obstruction, popliteal valve reflux, and most important, ipsilateral recurrent DVT.[15]

Dr Tazi Mezalek. The risk and severity of PTS depend on the characteristics of the triggering DVT at baseline and the resolution or persistence of the thrombus during follow-up.[5-7,29-31] Other factors increase the risk of PTS, like elevated body mass index, advanced age, and the severity of symptoms at the onset of DVT.[30-32] Preexisting primary CVD and varicose veins appear to be associated with an increased risk of VTE and, consequently, PTS.[30] However, some authors have expressed concern that some of those patients with CVI may have had prior undiagnosed episodes of VTE. The extensive proximal nature of the DVT is an important parameter. The more proximal and extensive DVT provides a higher risk of PTS.[30,31] The risk of PTS is 2- to 3-fold higher after iliac or iliofemoral thrombosis than more distal DVT.[30-32]

During follow-up, persistent venous symptoms 1 month after acute DVT appear to increase the risk of subsequent PTS.[6,33] Moreover, ultrasound parameters measured 1 or 2 months after a proximal DVT proved to be predictive of PTS: residual thrombosis (odds ratio, 2.17) and popliteal reflux (odds ratio, 1.34).[34]

Finally, recurrent ipsilateral DVT is one of the most important risk factors, increasing the PTS risk by 4- to 6-fold.[29,30,34] Therefore, prevention of recurrent thrombotic events is the cornerstone of PTS prevention and raises the question of the duration of anticoagulation.

Dr Lobastov. Risk factors for PTS are well established with calculated risk ratios or odds ratios.[3] In descending order of their impact, they are as follows: ipsilateral DVT recurrence (risk of 1.6-9.6), elevated levels of inflammatory biomarkers (risk of 1.4-8.0), proximal DVT localization (risk of 1.5-6.3), older age (risk of 0.6-3.9), obesity (risk of 1.1-3.5), varicose veins at baseline (risk of 1.5-3.2), inadequate anticoagulation (risk of 1.8-2.7), and residual venous obstruction (RVO; risk of 1.6-2.1).

Does the quality of initial anticoagulation for DVT reduce the incidence of PTS?

Dr Geroulakos. If the quality of initial anticoagulation is inadequate, this could lead to the recurrence of the DVT and more extensive venous damage resulting in a higher probability of PTS.

Dr Josnin. Studies published today show that poor anticoagulation is a risk factor for PTS.[35] However, more studies are needed to understand better which type of anticoagulation is the most appropriate and to discuss the sequence of this treatment.

Dr Kan. In answer to the question whether the quality of initial anticoagulation for DVT reduces the incidence of PTS, I think it's related. There is a 3-fold increased risk of PTS if anticoagulant levels are insufficient (eg, international normalized ratio [INR] >50% below therapeutic levels) during the first 3 months of vitamin K antagonist (VKA) therapy. Whether treatment of DVT with dual oral anticoagulants (DOACs) affects the risk of PTS compared with treatment with low molecular weight heparin (LMWH) or VKA is unknown. A meta-analysis of available data suggests that treatment of DVT with prolonged LMWH monotherapy may reduce the incidence of PTS compared with a short-term LMWH treatment for 5 to 7 days, followed by VKA. Large multicenter trials using validated diagnostic criteria for PTS are needed to confirm the effectiveness of prolonged LMWH in patients at high risk of PTS and to assess the efficacy of DOACs in preventing PTS.[28] The best way to prevent PTS is to prevent DVT with pharmacologic or mechanical thromboprophylaxis in high-risk patients and settings.

Dr Tazi Mezalek. During the first 3 months of treatment with VKA, inadequate control of the INR increases the risk of PTS 2-fold.[35] Some data suggest that long-term treatment with LMWH may lead to lower rates of PTS in comparison with VKA.[36] Otherwise, DOACs for the initial treatment of DVT are associated with a lower incidence of residual vein thrombosis than VKA.[37] In a recent publication, rivaroxaban significantly reduced PTS risk compared with warfarin.[38] After adjusting for baseline characteristics, the risk of PTS in the DOAC-treated group was reduced by 54%.[37,38] A recent meta-analysis of all available studies addressing this issue confirmed that rivaroxaban was found to significantly reduce the incidence of PTS compared with VKA and also was likely to prevent severe forms of PTS.[39]

Dr Lobastov. Adequate anticoagulation in terms of preventing thrombus extension and protection of the venous wall in the acute phase of thrombosis, as well as prophylaxis of DVT recurrence and improving recanalization, is a cornerstone for PTS prevention. Emerging evidence suggests that treatment with rivaroxaban, compared with VKA, significantly reduces PTS risk by 46% to 48% and severe PTS by 45% to 51%.[40,41] However, this is not a common effect for all DOACs. No evidence is available for apixaban, but edoxaban and dabigatran do not affect PTS risk.[42,43] Notable, in the ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis), early start of rivaroxaban within the first 10 days was associated with a 47% reduction in risk of PTS.[44] So, it seems to be crucial to give adequate anticoagulation during the acute phase of DVT.

Does early catheter-directed thrombolysis prevent PTS?

Dr Geroulakos. The ATTRACT trial has shown that early catheter-directed thrombolysis (CDT) reduces the incidence of severe PTS.[45]

Dr Josnin. Thrombolysis remains a treatment that is decided on a case-by-case basis according to precise criteria, but it has proven its effectiveness.

Dr Kan. Upfront thrombolytic therapy combined with heparin for acute DVT resulted in higher venous patency rates and better valvular function preservation than using heparin alone. CDT or pharmacomechanical CDT (PCDT) may be safer and more effective than systemic thrombolysis. It may prove to be a promising technique for preventing PTS after proximal DVT.

According to the trial results by Enden T et al, the use of additional CDT in anticoagulated patients with acute DVT involving the iliac and/or common femoral veins showed a statistically significant 2-year PTS risk reduction at the expense of a 3% increase in major bleeding.[4] However, 41% of patients with CDT still developed PTS, suggesting that it did not eliminate the risk of PTS and did not improve QOL at 2 to 5 years of follow-up. The CAVA trial (Ultrasound-Accelerated Catheter-Directed Thrombolysis Versus Anticoagulation for the Prevention of Post-Thrombotic Syndrome) did not show a reduction in PTS after additional ultrasound-accelerated CDT in patients with acute iliofemoral DVT at 1-year follow-up.[46] Susan Kahn recommends these techniques in patients on a case-by-case basis: those with extensive (eg, iliofemoral) thrombosis and who are recently (ie, ≤14 days) symptomatic, with low bleeding risk, and life expectancy of at least 1 year.[28]

Dr Nikolov. Unfortunately, there is no clear evidence. However, in 2019, the NICE guidelines acknowledged that percutaneous mechanical thrombectomy (PMT) could be used for patients with acute iliofemoral DVT with special arrangements for informed consent, local governance, and quality improvement, though it remains investigational for femoropopliteal DVT.[47] The 2020 American Society of Hematology guidelines state that thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic DVT involving the iliac vein and common femoral vein, but that its use should be rare for femoropopliteal DVT.[48] In 2021, the European Society of Vascular Surgery issued guidelines recommending early thrombus removal strategies for selected patients with acute iliofemoral DVT but not for less extensive DVT.[49] Nowadays, CDT is indicated mostly for patients with acute iliofemoral DVT, severe symptoms, low bleeding risk, and good functional status.[50]

Dr Tazi Mezalek. Early thrombus removal by surgical or instrumental thrombectomy was popularized many years ago. Because iliofemoral DVT is associated with severe forms of PTS, it has been suggested that early surgical removal of thrombus may be beneficial in certain conditions.[51] Meanwhile, the demonstration that surgical thrombectomy prevents PTS is not yet validated.

The association of upfront heparin and systemic thrombolytic therapy to treat DVT leads to higher rates of vein patency and better preservation of valve function than using heparin alone.[52] CDT is likely to be safer, is also associated with improved venous patency and valve preservation, and may reduce the incidence of PTS compared with conventional anticoagulation alone.[53] Three randomized controlled clinical trials (RCTs) on this topic have been published, with conflicting results.[45,46,54] Globally, the additional use of CDT had no benefit over anticoagulation alone in preventing PTS, with a higher major rate of bleeding. However, subgroup analysis showed a benefit in reducing severe PTS, limited to patients with iliofemoral DVT.[55]

Dr Lobastov. Despite discouraging results of ATTRACT and CAVA trials, the meta-analysis considering their data demonstrates a significant PTS risk reduction by 22% after thrombolysis.[56] Of course, there is a lot of criticism of the last RCTs due to low technical success (76% in ATTRACT and 53% in CAVA), low rate of venous stenting for residual obstruction (28% in ATTRACT and 45% in CAVA), enrolment of patients with femoropopliteal DVT, and nonoptimal anticoagulation with a high rate of recurrent DVT (10% in ATTRACT and 5.5% in CAVA).[45,46] So, selecting patients that would receive maximal technical success and clinical benefits from CDT remains a crucial question. Post hoc analysis of the CAVA trial showed that patients with acute and subacute thrombosis assessed by results of magnetic resonance venography (MRV) and clinical presentation had an 11 times higher success rate after ultrasound-accelerated thrombolysis.[57] The recent consensus by the Society of Interventional Radiology stated that CDT/PCDT is suggested for the following: (i) patients with iliofemoral DVT and acute limb-threatening circulatory compromise (eg, phlegmasia cerulea dolens); ii) nonelderly patients at low bleeding risk with acute iliofemoral DVT and nonthreatening limb and who have moderate-to-severe symptoms; and iii) patients with acute iliofemoral DVT who continue to have moderate-to-severe symptoms or impaired ambulation despite initial anticoagulation, who are at low risk of bleeding, and whose thrombus is believed to have formed within the past

14 days.[58] So, interventional treatment is considered for acute presentation of proximal DVT and patients with poor response to standard anticoagulation. It is probable that those patients with poor response to standard anticoagulation may receive additional benefits from CDT/PCDT.

Can elastic compression stockings prevent PTS?

Dr Geroulakos. We and others have shown that elastic compression stockings (ECS) can significantly reduce the incidence of PTS after DVT, and therefore these should be routinely prescribed.[59]

Dr Josnin. The SOX study (Compression Stockings to Prevent the Post-Thrombotic Syndrome After Symptomatic Proximal Deep Venous Thrombosis) has profoundly changed our habits, and until now, we've recommended wearing ECS for 2 years after a venous thrombosis. However, the SOX study showed an apparent decrease in treatment adherence with ECS compared with other studies.[60] This finding has generated doubts about the benefits of prolonged compression treatment after DVT. So current guidelines recommend wearing compression to relieve symptoms in the acute phase, and further studies are needed to make progress on this subject. In my practice, prescribing compression remains systematic.

Dr Kan. ECS can prevent PTS by reducing leg swelling and venous hypertension. However, there is conflicting evidence regarding the long-term effectiveness of ECS in preventing PTS. Evidence-based consensus guidelines recommend using ECS for at least 2 years after DVT to prevent PTS, a recommendation based on the results of small open-label trials.[28]

However, the SOX trial showed no evidence that active compression stockings help prevent PTS, reduce the risk of recurrent VTE, or improve QOL.[60] A meta-analysis including data from the SOX trial reported a combined hazard ratio of 0.69 (95% CI, 0.47-1.02) for developing PTS with ECS.[61] However, the authors caution that confidence in this pooled estimate is very low due to heterogeneity and inclusion of unblinded studies at high risk of bias and that the highest quality evidence recently available shows no effect of ECS on PTS. Based on these data, recent guidelines recommend against the routine use of ECS for prevention of PTS.[28]

Although unlikely to cause harm, ESC can be difficult to apply, uncomfortable, expensive, and must be replaced every few months. Given current evidence, not all patients with DVT require routine use of ECS that must continue until symptoms improve.[28]

Dr Nikolov. All current evidence suggests that ECS are beneficial in preventing PTS after DVT.[15]

Dr Tazi Mezalek. Effective compression has been shown to reduce venous hypertension, edema, to minimize microcirculatory changes, and to plausibly play a role in preventing PTS.[62] A 2017 Cochrane systematic review concluded that there was a trend favoring the use of ECS after DVT (RR, 0.62; 95% CI, 0.38-1.01); however, there were methodological limitations in the included trials.[63]

Dr Lobastov. Many discussions were raised around the SOX trial.[60] It was criticized for placebo stockings, delayed start of compression, low compliance, and many other issues. Further trials showed that the early start of elastic compression in the acute phase of DVT prevents PTS signs such as skin induration, hyperpigmentation, venous ectasia, and pain with calf compression.[64] So, removing acute edema in DVT to protect lymphatic outflow is crucial because damage to lymphatic vessels seems to play a pivotal role in PTS development.[65-67] Considering placebo stockings with a pressure of 5 mm Hg, a previous trial showed that such pressure is enough to prevent occupational edema.[68] Moreover, progressive ECS with increased pressure at the wide part of the calf may be more effective than classical graduated ECS.[69,70] So, the results of the SOX trial could be interpreted as evidence that low-pressure compression stockings are noninferior to high-pressure ones in terms of PTS development. This idea could be partially confirmed by the results of the recent CELEST trial *(Compression Elastique Evaluation du Syndrome post Thrombotique)*, which found stockings of 25 mm Hg noninferior to 35 mm Hg for PTS occurrence within 2 years after DVT.[71] At the same time, 2 studies (OCTAVIA [Optimal duration of Compression Therapy As prevention of chronic Venous Insufficiency After deep venous thrombosis] and IDEAL DVT [Individually Tailored Elastic Compression Therapy After Deep Venous Thrombosis in Relation to the Incidence of Post Thrombotic Syndrome]) showed no need for permanent use of ECS for 2 years in persons with no PTS symptoms at 6 to 12 months after DVT.[72,73] Considering all these findings, the latest guidelines still recommend using ECS for at least 12 months to prevent PTS after proximal DVT.[49]

How long should patients with PTS be treated with anticoagulants?

Dr Josnin. The importance of anticoagulant therapy in preventing PTS is undeniable, with the American Heart Association recommendations clearly emphasizing this.[3] However, the type of treatment is not as clearly defined. Studies tend to show that LMWH are better at preventing PTS than VKA and DOAC as well. Some investigators consider that the anti-inflammatory role of LMWH would indicate its use in the initial phase of treatment.

Dr Kan. Timely and effective anticoagulant therapy is the best way to prevent PTS after acute DVT. Data suggest that LMWH and DOACs may be superior to VKA in preventing PTS, and the anti-inflammatory properties of LMWH and DOAC may drive this improved efficacy. LMWH appear to have stronger anti-inflammatory properties than DOACs, but direct comparisons in PTS prevention are still lacking.[74]

Thrombus regression in acute DVT has been shown to be rapid during the first 2 to 3 months after initiation of anticoagulant therapy and to slow gradually after 3 months. After 2 years, no additional thrombus is expected to resolve, and the extent of residual venous obstruction (RVO) is fixed.

From a hemodynamic point of view, better and earlier thrombolytic conditions lead to better valve protection and reduced venous valve regurgitation. In addition, the smaller the clot burden, the lower the risk of developing RVO, venous reflux, and ultimately PTS. This is the rationale for using CDT in extensive DVT, but any treatment that reduces the initial clot burden should reduce the risk of PTS. This may be why all anticoagulant treatments are effective in preventing PTS.[74]

Dr Tazi Mezalek. Given the parietal alteration, venous reflux, and obstruction attributed to PTS, it has been suggested that patients with PTS may be at increased risk for VTE recurrence, independent of other risk factors. The data in the literature are conflicting. In one study, RVO was accompanied by a 2-fold increased risk of VTE recurrence after 3 months of conventional anticoagulant therapy.[75] In contrast, Prandoni et al followed approximately 900 patients with proximal DVT and reported a hazard ratio of DVT recurrence in patients with PTS of 1.14, suggesting that PTS is not associated with an increased risk of recurrent VTE.[76] However, some authors suggest that DUS may help determine the appropriate discontinuation of anticoagulant therapy in selected patients.[49] A limitation of this approach is that routine measurement of residual thrombosis is difficult to standardize. Extended anticoagulation with DOACs at either a treatment or prophylactic dose reduces the risk of recurrent VTE without affecting major bleeding. It may represent an acceptable strategy to prevent future VTE recurrence in case of PTS and/or residual thrombosis after 3 to 6 months of conventional anticoagulation.

Dr Lobastov. PTS and VTE recurrence have a close relationship. New DVT is associated with an approximately 10-fold increase in the risk of PTS development, whereas PTS increases the risk of recurrent VTE by 2.5- to 3-fold.[3,77] Moreover, such factors as RVO, elevated D-dimer, and obesity affect both risks.

According to the current guidelines, any VTE event should be treated with anticoagulation for at least 3 months.[49,78,79] The further decision for indefinite anticoagulation should be based on the individual assessment of risks (major bleeding) and benefits (prevention of VTE recurrence). DOACs appeared to be very safe during prolonged anticoagulation. Compared with placebo, they reduce overall mortality by 61% by decreasing the risk of VTE recurrence, including fatal pulmonary embolism, without increasing the risk of major bleeding, including fatal hemorrhage.[80] That's why current guidelines tend to prolong anticoagulation with DOACs in most patients at risk of recurrent VTE.

Individual risk of recurrence is determined by different factors, of which the most important is a clinical provocation of the index VTE. Suppose DVT is provoked by a major transient risk factor (major surgery, trauma with fractures, confined to bed in the hospital for ≥3 days). In that case, the risk of recurrence is the lowest, and anticoagulation may be stopped after 3 months. Also, in VTE provoked by pregnancy and oral contraceptives (formally, minor transient risk factor), the risk of recurrence is low (<3% per year) in the absence of new pregnancies and contraceptive pills, so anticoagulation may be stopped.[49,81] In all other cases of VTE provoked by minor transient (minor surgery, leg trauma without fracture with reduced mobility, long-haul flights, admission to hospital for <3 days with an acute illness, confined to bed out of the hospital ≥3 days) and minor persistent (inflammatory bowel disease, active autoimmune disease, leg paralysis, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, obesity, etc) risk factors or in cases of VTE that are clinically unprovoked, indefinite anticoagulation is recommended as long as well tolerated.[49,78,79,82] Prolonged anticoagulation is strongly indicated in individuals at high risk of recurrence (>8% per year) such as the following: repeated VTE in the absence of major transient risk factors, active cancer, and antiphospholipid syndrome.

Thus, in the current case of unprovoked DVT with good treatment tolerability, indefinite anticoagulation with a reduced dose of DOAC is indicated.

What is the best approach to treat established PTS?

Dr Geroulakos. This would be treatment with micronized purified flavonoid fraction (MPFF), ECS, analgesia, and iliac stenting, if appropriate.

Dr Josnin. Physical exercises are indicated, although studies with larger cohorts are still needed.[83] ECS is indicated, but the strength of this compression must be adapted to the patient's clinical response and improvement in QOL. Concerning MPFF, a study is underway, the MUFFIN-PTS trial (Micronized Purified Flavonoid Fraction for the Treatment of Post-Thrombotic Syndrome), with results pending.[84]

Dr Kan. The management cornerstones for patients with established PTS are ECS, exercise, and lifestyle changes.[85] Every day, wearing a knee-length ECS of 20 to 30 mm Hg is recommended for patients with established PTS. For patients with moderate-to-severe PTS whose symptoms are not adequately controlled with ECS alone, it is also recommended to try intermittent compression devices. A supervised exercise training program of 6 months or longer is reasonable for patients with PTS who can tolerate it. A multidisciplinary approach is recommended for the management of postthrombotic ulcers.[86] In refractory cases, surgery or endovascular intervention may be considered. However, due to the lack of effective treatments, new approaches are needed to prevent and treat PTS.

Dr Nikolov. The first line of treatment is lifestyle modification, exercises, ECS, and venoactive drugs (VADs). The second line is invasive endovenous techniques, such as different ablation modalities for superficial reflux and venous stenting for chronic iliac vein occlusions.

Dr Tazi Mezalek. Support options for PTS are limited. Recently, evidence-based guidelines focused on PTS were published.[3,15,86,87] The recommendations are based on a few controlled studies with a limited number of patients and limited follow-up time.

In contrast to the uncertainty surrounding ECS use for PTS prevention, they are the cornerstone of treatment in PTS to reduce symptoms. However, their use is based primarily on extrapolation of results from patients with primary CVD and a low risk of harm.[88,89] The optimal degree of compression is unknown, and guidelines suggest prescribing knee-length 20-30-mm-Hg ESC to patients with PTS-related leg heaviness or swelling. If 20-30-mm-Hg ECS is not effective enough, a stronger pressure stocking (30-40 mm Hg; or ≥40 mm Hg) can be tried. Intermittent pneumatic compression can also be used with severe symptoms and edema in PTS.[90] Walking exercise implemented early after DVT diagnosis, associated with early compression, reduces DVT-related symptoms. A 6-month walking exercise program should be encouraged to enhance calf muscle contractions and plantar loading to enhance venous drainage and then improve PTS severity, and QOL, with no adverse events.[91]

Several reports have demonstrated promising clinical response and durability of recanalization and venous stenting for chronic iliocaval obstructions in selected PTS patients.[92] Experience with these procedures varies substantially. Complications and failure rates are uncertain, and it remains difficult to identify which patients would benefit most.

One treatment option to explore is the use of VADs. Four randomized trials have been performed to evaluate the effectiveness of VADs for PTS (rutosides, defibrotide, and hidrosmine). Overall, low-quality evidence supports the use of VADs to treat PTS.[93] Among the VADs that could be tested, MPFF seems to have a favorable profile. It acts to improve venous obstruction, valvular reflux, and inflammatory venous lesions, which are vital contributors to the pathogenesis of PTS. This molecule appears promising, especially since it improves clinical manifestations, QOL, and objective venous parameters of CVD.[94] Observational studies have reported that MPFF improved clinical manifestations or objective venous measures in patients with PTS.[95] When combined with rivaroxaban in femoropopliteal DVT, MPFF improved the Villalta score and the venous clinical severity score and decreased the incidence of PTS in DVT patients compared with rivaroxaban alone.[96] However, there is a lack of high-quality confirmatory studies to strengthen the evidence for using venotonic drugs to treat PTS.

Dr Lobastov. Today, there is a lack of direct evidence on the efficacy and safety of different treatment approaches in PTS. Exercises, ECS, VADs, and intermittent pneumatic compression are traditionally recommended to improve symptoms and signs of PTS.[3,28,85,97,98] However, the majority of these recommendations are driven by nonspecific studies in CVD patients, which may include unselected populations with postthrombotic reflux and obstruction. MPFF has a high potential to be beneficial in PTS because it controls symptoms and signs of CVD and improves deep vein recanalization due to topical anti-inflammatory activity in the vein wall.[94,96,99,100] In addition, electrical calf muscle stimulation may be recommended at the top of standard therapy for further improvement of symptoms, recanalization, and prevention of VTE recurrence.[101]

Conclusion

- The best way to prevent PTS is to prevent DVT occurrence and ipsilateral recurrence with pharmacologic primary and secondary prophylaxis in high-risk patients.
- Clinical scales may help predict the development of PTS after proximal DVT.
- Anticoagulation with DOACs rather than VKA may reduce the development of PTS.
- Careful consideration for CDT/PCDT in patients with iliofemoral DVT, moderate-to-severe symptoms, and low risk of bleeding may help to prevent PTS.
- Using ECS after DVT can prevent PTS, but the evidence is conflicting. Individual adjustment of treatment duration according to the symptoms of PTS is recommended. Early compression starting in the acute phase of DVT, and maintenance of high adherence to ECS use is essential for PTS prevention.
- The nature of index DVT should drive the duration of anticoagulation treatment. In the absence of a major transient risk factor, indefinite anticoagulation with DOACs is indicated in most patients.
- MPFF has a high potential in PTS prevention and treatment, but direct evidence is still neeed.

CORRESPONDING AUTHOR

Zoubida Tazi Mezalek

Department of Clinical Hematology, Internal Medicine, Mohammed V University, Ibn Sina Hospital, Rabat, Morocco

EMAIL: *z.tazimezalek@gmail.com*

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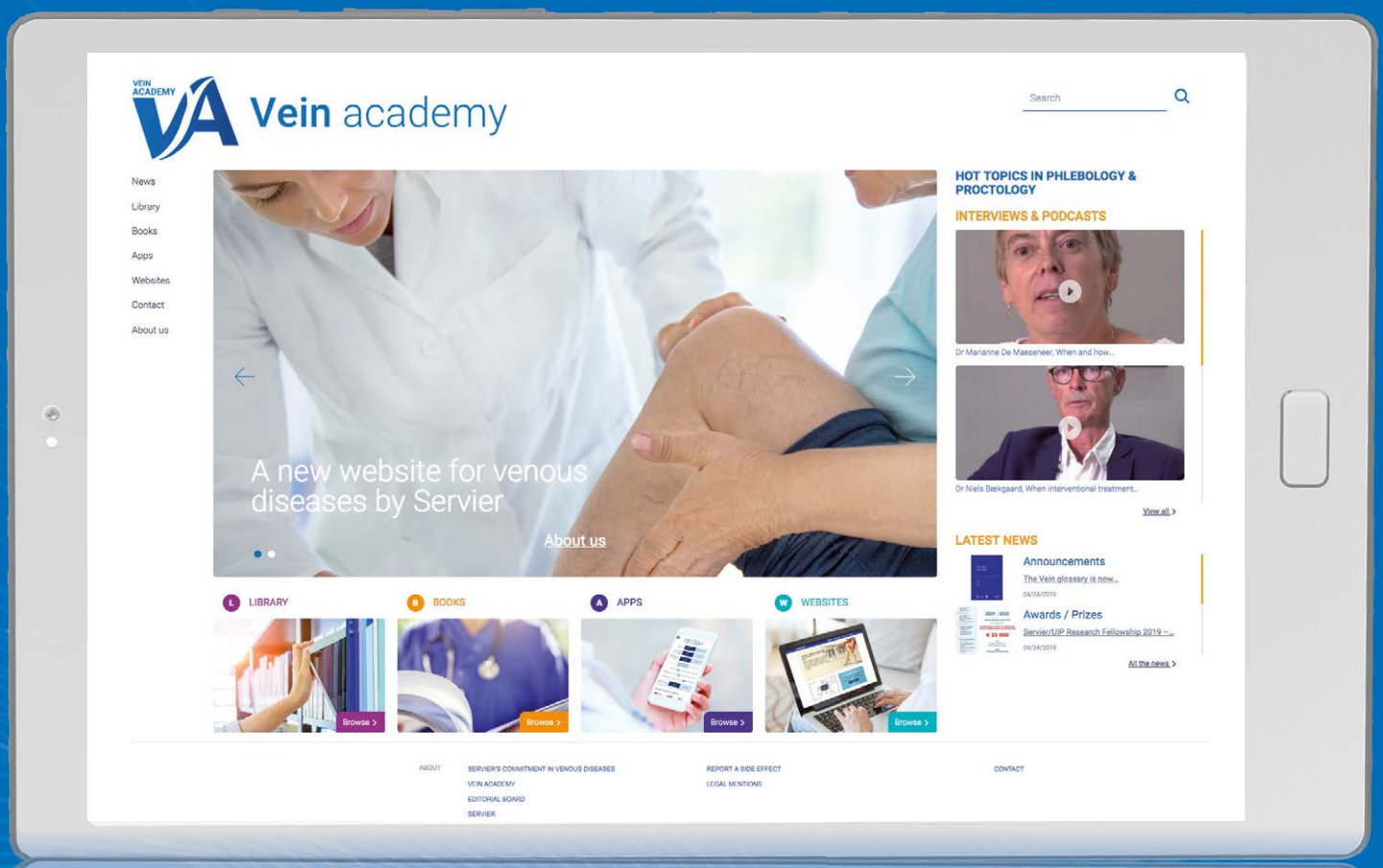

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